SURGERY

VOL. 9 MARCH, 1941 NO. 3

Original Communications

CHRONIC ABDOMINAL PAIN DUE TO HYPOGLYCEMIA

WITH A NOTE ON THE PATHOGENESIS OF NEUROTIC SYMPTOMATOLOGY

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THIS report describes a group of five patients who had long histories of recurrent attacks of abdominal pain due to unrecognized hypoglycemia. All had undergone thorough investigations in which all possible procedures were employed with the exception of the glucose tolerance test. Laparotomy was advised as a last resort. Appendectomy was performed three times; cholecystectomy and herniorrhaphy, once each. However, pain recurred and when the patients returned with their original complaints it was thought that they were confirmed neurotics or that they had postoperative adhesions. In addition to the pain the patients had neurologic manifestations of hypoglycemia which were not accorded their proper significance. Such manifestations were headache, nervousness, dizziness, sweats, faintness, and syncope. No doubt the recital of such complaints by a patient with abdominal pain would serve to stamp him as a neurotic, a term which is much overworked in medicine. If such symptoms are interpreted as hypoglycemic manifestations the true nature of the syndrome will become clear. Two female patients in the group had headaches of such frequency and severity as to necessitate investigation for brain tumor. One of these patients went through encephalography twice.

Hypoglycemia as a cause of abdominal pain has been reported by various authors.[1-6] The most successful form of therapy has been the employment of low carbohydrate diets with increased protein and fat (carbohydrate, 75 to 100 Gm.; protein, 75 to 125 Gm.; fat, 100 to 150 Gm.). Between meals and at bedtime the patient is instructed to take a glass of milk or milk and cream or tomato juice, with a cracker and butter or cheese. Bedtime feeding is especially indicated in cases of nocturnal pain. Relief from pain may be attained after a few days or

Received for publication, April 22, 1940.

weeks, because such a diet elevates and stabilizes blood sugar levels (Fig. 1).

As to the mechanism responsible for the abdominal pain, the experimental injection of insulin into normal human beings and dogs has yielded pertinent data. Bulatao and Carlson[7] injected twenty to forty units of insulin subcutaneously into dogs. When the blood sugar was between 80 and 70 mg. there was an increase in gastric tone and in the height and frequency of contractions, gradually developing into tetany. They state that "as the blood sugar falls to convulsion level the stomach motor mechanism usually shows alternate periods of atony and tetany,

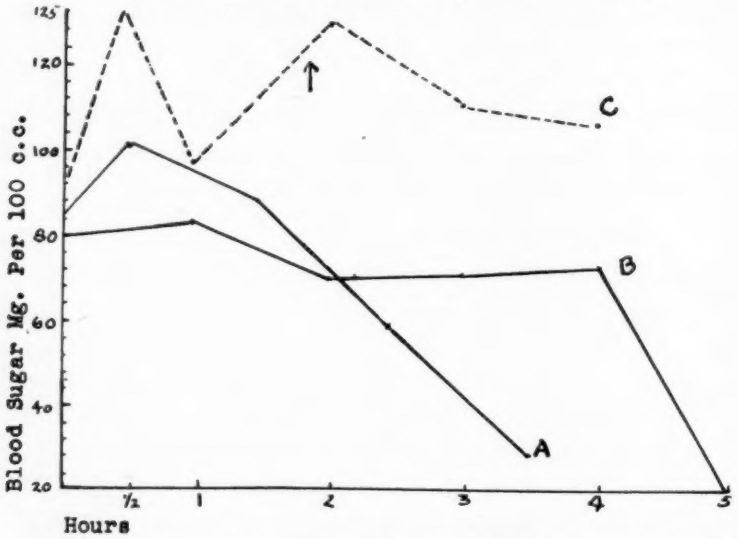

Fig. 1.—The effect of various meals on the blood sugar in a patient with chronic hypoglycemia whose chief complaint was severe headache. This patient is not included in the five cases reported in detail, but the response of the blood sugar to the various meals is typical of the response obtained in all patients investigated. Curve A shows the glucose tolerance after 100 Gm. of glucose; Curve B shows the course of the blood sugar after a high carbohydrate meal consisting of one orange, a bowl of oatmeal, two rolls, and a cup of sweetened coffee; Curve C shows the course after a low carbohydrate meal consisting of one orange, two eggs, one thin slice of bread and butter, a glass of milk to which 1 oz. of cream was added. About two hours after this meal the patient took a glass of milk.

the inhibition predominating." Quigley, Johnson, and Solomon[8] injected twelve to twenty units of insulin into normal fasting human beings. In about forty-five to ninety minutes following the injection subjective sensations, such as restlessness, weakness, hunger, and sweating, appeared. Soon there was increased gastric motility and as this became more marked subjective sensations with an "uncomfortable feeling of tension or pressure or pain referred to the stomach" often accompanied by lassitude or weakness appeared. Headache, nervousness, dizziness, vasomotor instability, irritability, and ill temper may appear. Subjective symptoms passed off after the subjects took fruit juice. They observed that "in persons with more stable nervous organization strong hunger may be present without the other accessory phenomena except hyperexcitability, and, conversely, in some persons the feeling of weakness and headache may be so marked as to crowd out the hunger pangs."

These investigators concluded that the hypoglycemia affects the central nervous system and stimuli reach the abdominal viscera through the vagus. La Barre and Destree[9] found that a fall to 75 mg. in human beings stimulated gastric contractions; whereas, a fall to 45 mg. caused gastric atony.

From such experimental data one may justifiably attribute abdominal pain and nervous symptoms in patients with hypoglycemia to the abnormal fall in blood sugar concentration. The fact that a low carbohydrate diet by overcoming such abnormal behavior in blood sugar regulation can prevent the attacks is further confirmation that such a mechanism is responsible for the pain. These patients usually have relief from pain on taking food. Such relief may be attributed to the rise in blood sugar that follows the ingestion of food. Spontaneous relief from pain may be attributed to the rise in blood sugar that follows the mobilization of glucose from liver glycogen by the liberation of adrenalin, a protective mechanism which comes into play at hypoglycemic levels.[10] It is generally accepted that symptoms, such as tremors, sweating, pallor, tachycardia, and palpitation, occurring during hypoglycemic episodes, are actually due to such adrenal-sympathetic activity and may be regarded as unpleasant side reactions accompanying the essential glycogenolytic action of adrenalin.

The pain in hypoglycemic patients may be generalized or localized. It may be localized to the epigastrium, to the right upper quadrant with radiation to the back and shoulder, to either of the lower quadrants, or to the lower half of the abdomen. Apparently in each patient the hypoglycemia has a tendency to stimulate the same group of neurons in the vagal nucleus, and the particular segment of the gastrointestinal tract (including the biliary tract) innervated by these neurons undergoes strong contraction, which may even become tetanic.

As long as the patients remained on a low carbohydrate diet they had no pain. Whenever they went back to their former high carbohydrate intake they usually had recurrence after several days. This is to be expected since it has been demonstrated that a high carbohydrate intake increases sugar tolerance with resultant lowering of blood sugar levels.[11]

It is not within the scope of this paper to enter into a detailed discussion of the mechanism whereby a low carbohydrate diet actually brings about higher blood sugar levels. However, some consideration of the explanations that have been offered is in order. When Harris first coined the term hyperinsulinism he implied that patients with this disorder suffered an extra discharge of insulin on the ingestion of carbohydrate rich foods, such discharge resulting in hypoglycemia. On a low carbohydrate diet such stimulation of the pancreas and hypoglycemia would be avoided. Since a low carbohydrate diet usually relieves the symptoms of hypoglycemia and since it actually brings about higher blood sugar levels, such an explanation seems tenable. Recently, Soskin and co-workers[12, 13] have shown that the rate of discharge of

glucose from the liver is an important factor in the regulation of blood sugar levels. During the fasting state the blood sugar is derived wholly from the breakdown of liver glycogen. These workers found that when glucose was injected intravenously into a dog the liver output of glucose was inhibited and was not resumed at its usual rate until the blood sugar level had fallen to the previous fasting value. They further found that the greater the amount of glucose injected, the greater the inhibition of liver output. Further, if the inhibition was great enough the resumption of liver output may be delayed long enough to permit the blood sugar to fall to hypoglycemic levels. These workers also showed that such hypoglycemia was not due to an extra discharge of insulin.

Applying these experimental findings to patients with chronic hypoglycemia one may state that the ingestion of carbohydrate rich foods inhibits the liver output of glucose to such an extent as to bring about hypoglycemia. On a low carbohydrate intake such suppression of liver output is avoided and subsequent hypoglycemia prevented. During the fasting state the blood sugar is maintained by the breakdown of liver glycogen. It is obvious that the amount of glycogen stored in the liver will determine the amount of glucose liberated into the blood stream and the ultimate blood sugar level. A glycogen poor liver will thus be an important factor in the production of hypoglycemia.

It has also been established that tissues consume oxygen in proportion as they utilize glucose. This is especially so in the case of tissues with respiratory quotients of unity, such as the brain, which burns glucose practically exclusively for energy purposes. Dameshek, Myerson, and Stephenson[14] found that during insulin hypoglycemia in man there was a diminished oxygen consumption by the brain. Himwich and Fazekas[15] found that during insulin hypoglycemia in dogs there was a considerable fall in the oxygen consumption of the brain. Holmes,[16] Dickens and Greville,[17] and Wortis,[18] using the Barcroft-Warburg technique, found that the oxygen consumption of excised pieces of brain, spinal cord, heart, testis, kidney, and spleen fell as the amount of glucose in the nutrient medium was reduced. During hypoglycemia, in patients with this disorder, there will be an asphyxia of the brain of mild, moderate, or severe degree, depending on the degree of hypoglycemia. This reduction in oxygen consumption of the brain will readily explain the many and varied neurologic and so-called neurotic symptoms associated with hypoglycemia.

Fortunately hypoglycemia and its symptoms are reversible. However, fatal cases have been reported and cerebral lesions, especially hemorrhages, have been observed.[19] I mention this matter of hemorrhage because patients with hypoglycemia show a tendency to bleed, manifest clinically as epistaxis, the coughing-up of clots, coffee-ground vomitus, tarry stools, and occasionally frank rectal bleeding. Such bleeding disappears when treatment for the metabolic disorder is instituted. The bleeding is capillary in origin, although it may be profuse at times.

The capillary wall itself must suffer some injury as a result of the metabolic disturbance. Increased capillary permeability with escape of fluid into surrounding brain tissues may explain the headache of hypoglycemia. The relief from headache frequently obtained with coal-tar drugs, such as aspirin, may be due to the fact that one of the effects of such drugs is their ability to raise the blood sugar.

CASE REPORTS

CASE 1.—S. P., white male, aged 41 years, first attended the medical clinic in July, 1936, because of frequent attacks of abdominal pain of two months' duration. He had pneumonia at 9 years of age and gonorrhea at 16 years of age. He had a tonsillectomy in 1934 for frequent sore throats. In 1935 a urethral stricture had to be dilated. He was married, with a wife and four children living and well. He was a laundry worker. He smoked about ten cigarettes a day and took alcohol rarely.

In May, 1936, he began to have almost daily attacks of right-sided abdominal pain radiating to the lumbar region, usually coming on between 4:00 and 6:00 A.M., waking him from sleep. The pain was severe, and he would get up and walk about the room for about one-half hour until relieved. Sometimes the pain did not subside until he ate breakfast. Epigastric burning, belching, and sour eructations, but no vomiting, often accompanied the attacks. He also gave a history of tarry stools. He visited the clinic at frequent intervals during the summer of 1936. General physical and neurologic examinations revealed no abnormalities. The blood Wassermann test was negative. Blood counts and urinalyses were normal. Roentgen examinations of the gastrointestinal, biliary, and genito-urinary tracts revealed no abnormality. He was admitted to the surgical ward for further observation on Sept. 12, 1936. On the ward he had his usual attacks of pain and, since no further clues as to etiology were uncovered, an exploratory laparotomy was performed on Sept. 29 under general anesthesia. At operation no organic disease was demonstrable and a normal appendix was removed. His postoperative course was stormy. On the second day he had signs of a right middle lobe pneumonia with much distention and cramps. On Oct. 3 the wound was found gaping with visible coils of intestine. On Oct. 4 he had an attack of unconsciousness without convulsions. He improved slowly thereafter, although he sweated much at night. He was discharged on the thirty-fourth postoperative day. His attacks of pain promptly recurred and he returned to the clinic at frequent intervals during 1936 and 1937. He was first seen by me in August, 1937, still complaining of his pains. In view of the negative physical, laboratory, roentgenologic, and operative findings I regarded him as a neurotic and prescribed placebos, but without improvement. The patient was of phlegmatic temperament and not likely to be neurotic. In December, 1937, he complained of occipital headache, sweats, and attacks of faintness. These complaints were not of recent origin but had not been stressed by the patient because they were overshadowed by the abdominal symptoms. These nervous symptoms suggested hypoglycemic episodes and a glucose tolerance test on Dec. 22, 1937, revealed: fasting 54; one-half hour, 113; 1 hour, 92; 2 hours, 79; 3 hours, 35; 4 hours, 77. He was put on a low carbohydrate diet at once with feedings between meals and at bedtime. At the end of two weeks he reported that he had less belching and sour eructations and that the attacks of pain were fewer, less severe, and of shorter duration. At the end of four weeks he reported complete freedom from pain, belching, and eructations. The headaches and sweats became more infrequent and disappeared completely after two months. He had no more tarry stools. Now, after two years he continues symptom free.

Comment.—The occurrence of pain in this patient only during the early morning hours was due no doubt to the fact that the blood sugar reached its lowest level during the nocturnal fast. Blood sugar studies on other hypoglycemic patients with nocturnal symptoms have revealed that the occurrence of such symptoms coincides with low blood sugar levels at such times. Their occurrence at these hours may best be attributed to low liver glycogen reserves. As was stated previously, the blood sugar level during fast is maintained by the breakdown of liver glycogen. If such glycogen stores are low the blood sugar will not be maintained at normal levels; i.e., around 100 mg. The fact that it took about three weeks for his attacks of pain to cease completely and several weeks for his headaches and night sweats to disappear suggests that some profound bodily changes, such as an increase in glycogen stores, had to take place before blood sugar levels could be elevated and maintained at more normal levels. The attack of unconsciousness on the tenth postoperative day was undoubtedly a hypoglycemic episode, especially since the food intake was much reduced during this postoperative period and liver glycogen stores were further depleted. As to the evisceration I can only speculate. I have observed another patient, not included in this group, who had a blood sugar of 50 mg. during a tolerance test, and who two years before eviscerated following a cholecystectomy for gallstones. In view of the fact that cellular oxidations are reduced during hypoglycemia it is very likely that the metabolic processes concerned with growth and repair are not proceeding normally and the wound healing is delayed or defective. I have observed rapid healing of indolent infected wounds and ulcers following the institution of a low carbohydrate diet both in patients with frank hypoglycemia and in patients with more normal sugar levels. Benedict and Carpenter[20] have shown that there is a far greater oxygen consumption and heat production after the ingestion of protein rich foods than after the ingestion of carbohydrate rich foods.

CASE 2.—E. McC., white male, 50 years of age, first attended the medical clinic on May 22, 1937, complaining of frequent attacks of abdominal pain and vomiting of 1 year's duration. His past history revealed no major illnesses. He took no alcohol and smoked moderately. He had been employed as a restaurant worker. Because of loss of strength and marked tremors of the hands he was always dropping cups and glassware and had to quit his job.

The attacks of pain began in June, 1936. At that time they occurred at two-week intervals. As time went on the interval shortened so that by May, 1937, they were occurring every four to six days. The pain was generalized and severe, often radiating to the groins and testicles. Attacks lasted four to six hours, would disappear spontaneously, and would leave him prostrate. Vomiting always accompanied these bouts but did not relieve him. On questioning he said the vomitus sometimes resembled coffee grounds. During attacks he had a "dragging sensation" in the abdomen, felt faint, nervous, and had sweats. The attacks occurred only during the day and about three or four hours after a heavy meal. His appetite was good but he was afraid to eat since he noted that an attack was more

likely to follow a hearty meal. As a result he lost twenty-five pounds in twelve months' time. He also had had severe frontal headaches for several years.

Physical examination revealed a thin, nervous, apprehensive individual. Most of his teeth were missing. The thyroid gland was diffusely enlarged but not pulsating. There were coarse tremors of the outstretched hands, which were cold and damp. The heart and lungs were normal. The abdomen was soft and nontender. The liver edge was felt about two fingerbreadths below the right costal margin. There was a readily reducible incomplete left inguinal hernia of several years' duration. There were no abnormal neurologic signs. The clinical picture suggested hyperthyroidism but the basal metabolic rate was plus 1. The electrocardiogram revealed no abnormality. The blood Wassermann test was negative. Blood and urine examinations revealed no abnormalities. Roentgenologic and fluoroscopic examination of the gastrointestinal tract revealed no abnormality. He was hospitalized for further study on June 26, 1937. An attending physician made the following note: "The patient has a reducible left inguinal hernia, but I'm not sure that this is the cause of the abdominal pain, vomiting, and loss of 25 pounds." Two stool examinations were positive for occult blood. He had attacks of pain while on the ward. As a last resort, a hernia repair was advised, hoping to relieve him of his pain. He was operated upon July 9 under general anesthesia. His postoperative course was stormy. On July 20 his temperature rose to 104° F. with signs in the right chest of an early pneumonia. The wound became infected and he developed an ischiorectal abscess which had to be drained. He was discharged on the twenty-first postoperative day. His attacks of pain promptly recurred with the same frequency and intensity. He returned to the clinic at frequent intervals and was given various forms of medication without relief. He was first seen by me in January, 1938. Impressed with the history of headaches, nervousness, sweats, and feeling of faintness that accompanied the attacks of pain, a glucose tolerance test was done on Jan. 1, 1938. This revealed: fasting 75; one-half hour, 100; 1 hour, 95; 2 hours, 55; 3 hours, 45; 4 hours, 45. He was put at once on a low carbohydrate diet with between-meal feedings. In the ensuing four weeks he had only two attacks of pain, which were much less severe and of much shorter duration. After the fourth week the attacks ceased altogether and never recurred. At the end of two months he had gained 7 pounds and had fewer headaches, tremors, and sweats. His general nervousness and "shakiness" disappeared more slowly. Now, after two years, he has regained 20 pounds and has not had a single attack of pain in twenty-three months. He has been able to do hard manual labor without fatigue. Of course, he is still on a low carbohydrate diet.

Comment.—In contrast with Case 1 this patient had no nocturnal pain. His attacks would come on three or four hours after a "heavy meal," and for an individual on the relief roll a heavy meal contains much bread, potatoes, sugar, etc. In keeping with the explanation for the hypoglycemia offered by Soskin and his co-workers, one might say that the ingestion of the heavy meal suppressed markedly the liver output of glucose. The blood sugar values obtained in the tolerance test after 100 Gm. of glucose show a progressive fall after the first hour, reaching the low level of 45 mg. in the third and fourth hours. This paradoxical behavior of the blood sugar following the ingestion of 100 Gm. of glucose, in the present state of our knowledge, is best explained by the results of Soskin's work.

This patient's bouts of pain often lasted four to six hours before letting up. One might say that the adrenal-sympathetic mechanism was

deficient in that it failed to mobilize glucose from liver glycogen stores or that the glycogen stores were inadequate. Since his symptoms, such as tremors, nervousness, sweats, indicated adequate adrenal-sympathetic activity, it is more likely that the liver glycogen stores were depleted. Where liver glycogen stores are nearer normal, the bouts of pain should not last as long as six hours. The fact that patients, after being put on a low carbohydrate diet, have attacks of pain during the first few weeks, but of shorter duration and of lesser severity, suggests that the glycogen stores are being replenished so that when adrenalin is liberated in response to a fall in blood sugar the glycogenolytic response is adequate.

The patient's tremors, general nervousness, and sweats did not disappear completely until after five months, although they gradually lessened in severity after about two months. Since these symptoms are due most likely to sympathetic activity stimulated by the tendency to hypoglycemia, their disappearance depends on the restoration of the blood sugar to normal levels. The fact that the attacks of pain disappeared completely after four weeks suggests that a moderate elevation in blood sugar levels was sufficient to prevent pain but insufficient to relieve him of the nervous symptoms. It thus becomes evident that profound bodily changes must take place in order to bring about normal blood sugar regulation, and in some patients these changes can be accomplished only after several weeks or months.

This patient's postoperative course was also stormy. He had a right lower lobe pneumonia and a wound infection and developed an ischiorectal abscess which had to be drained.

The change in the physical and mental status in this patient after a year was most remarkable. The transformation from a thin, nervous, "jittery," apprehensive individual, incapacitated by pain and weakness, to a buoyant, robust, willing worker was most gratifying.

CASE 3.—S. R., white male, 36 years of age, single, was first seen in April, 1938, complaining of attacks of right upper quadrant pain since the age of 7 years. Past history revealed mild hydrocephalus in infancy and tonsillectomies at the ages of 7 and 18 years. The attacks of pain occurred every one to three weeks, lasted several hours, were accompanied by vomiting, and left him with a soreness in the upper abdomen that persisted for from twenty-four to thirty-six hours. The pain radiated to the right shoulder just as in biliary colic. There was never any jaundice. At the age of 21 years his gall bladder was removed at another institution. (It was impossible to get a description of the organ.) During the first postoperative week he had an attack of pain just like his previous ones. After discharge from the hospital the attacks recurred with the same frequency, intensity, and radiation. Between attacks he feels all right and can eat any kind of food. He has gone as long as five months without a seizure and feels best during the fall and early winter. In addition to the bouts of pain, he has, at irregular intervals, episodes of marked weakness, chills, pallor, and sweats. He also has frequent frontal headaches, cold sensations along both shins, numbness and cramps in both calves sometimes accompanied the episodes of weakness.

Physical examination revealed a thin, somewhat nervous, introspective individual. The head and neck were normal. The heart and lungs revealed no abnormality. The

blood pressure was 110/80. The abdomen revealed a well-healed right upper quadrant scar. There was no tenderness or rigidity. The extremities were normal. The blood Wassermann test was negative. Blood counts and urinalyses were normal. X-ray studies were not done since none was especially indicated. Chronic hypoglycemia was suspected because of the varied nervous symptoms. A glucose tolerance test done in April, 1938, revealed: fasting 65; one-half hour, 145; 1 hour, 100; 2 hours, 70; 3 hours, 70; 4 hours, 50. He was put on a low carbohydrate diet at once with feedings between meals. The attacks of pain stopped at once and he has had no further attacks up to the present time of writing, January, 1940. The episodes of weakness, chills, pallor, and sweats have likewise disappeared.

Comment.—The response to the change in diet in this patient was most dramatic in view of the twenty-nine-year history. The attacks stopped at once. It is very likely that the gall bladder removed was a normal one and the surgeon felt that its removal might relieve the patient of further pain simply because there would be no gall bladder present to contract. Since the localization and radiation of the pain after the operation were the same as before removal of the gall bladder, it is likely that the common duct, or the hepatic ducts, were being stimulated to strong contraction. That a correct diagnosis of chronic hypoglycemia should have been made in 1923 when the patient was operated upon is not to be expected since Harris published his first paper on the subject in 1924.

The patient's attacks began at the age of 7 years and occurred at intervals of one to three weeks. Between attacks he felt all right. If the bouts of pain were due to an inflammatory disease or stone, the course of the disease would have progressed in a few years to some stage requiring surgery. Pain due to biliary tract inflammation or stone does not manifest itself in this fashion over a long period of years. Now that the cause of the pain is definitely established, the syndrome could only have been caused by some labile mechanism that could come at intervals, cause much pain and discomfort for twenty-four to thirty-six hours, and then disappear. Such a reversible mechanism as a disturbance in blood sugar regulation fits in very well. While the patient had a chronic hypoglycemia, it may be said that the metabolic disturbance became aggravated periodically, at which time the hypoglycemia became more marked and brought on the bouts of pain. Since recovery from an attack was always spontaneous after twenty-four to thirty-six hours, such recovery may be attributed to the body's defense mechanisms capable of overcoming the hypoglycemia by mobilizing glycogen stores. Such mechanisms would be the adrenal-sympathetic system, the thyroid gland, and the anterior lobe of the pituitary. It is conceivable that these opposing hyperglycemic forces may respond beyond the point necessary to overcome the hypoglycemia and that their combined activity persists for several days or longer. The patient's diet with its high carbohydrate intake would then tend to increase the tolerance to glucose, depress the blood sugar levels again, and the cycle would be repeated.

CASE 4.—S. M., white female, 28 years of age, single, was first seen by me in December, 1938, complaining of attacks of epigastric and right lower quadrant pain and headaches of about seventeen years' duration. In recent years these had become almost daily occurrences. She had had the usual childhood diseases. Since the age of 11 years she had been subject to frequent attacks of abdominal pain, localized at times to the epigastrium and at times to the right lower quadrant. The pain in the epigastrium was cramplike, lasted a few minutes to one-half hour, was frequently accompanied by epigastric burning sensation and occasionally by nausea. She never vomited. The pain would come on one or two hours after a meal and disappear spontaneously. Sometimes she would get a sharp, severe, right lower quadrant pain lasting as long as two hours, accompanied by weakness, sweating, and dizziness. The headaches occurred almost daily and were described as "terrific." They were not localized to any specific part of the head.

The patient attended another clinic for several years because of her abdominal pain. Repeated physical examinations, various laboratory tests, and x-ray examinations of the gastrointestinal tract failed to yield clues as to the cause of her pain. An exploratory laparotomy was performed in September, 1934, and the appendix removed. The postoperative course was uneventful. The abdominal pain recurred shortly after she left the hospital. Pains and headaches continued during 1935, 1936, and 1937. In May, 1937, she spent two weeks at a leading neurologic clinic undergoing investigation for possible brain tumor. No evidence of tumor was obtained.

I first saw the patient in December, 1938. The history suggested chronic hypoglycemia as the most likely diagnosis. Examination revealed a moderately nervous, tense, worried individual. There were no abnormal physical signs. The abdomen was completely negative except for a well-healed scar. A glucose tolerance test revealed the flat type of curve: fasting 80; 1 hour, 85; 2 hours, 77; 3 hours, 80. She was put on a low carbohydrate diet. She was unable to take some food between meals because of the nature of her work. She was able to take some at bedtime. The abdominal pain stopped after one week. The headaches became milder and less frequent after two months but did not disappear completely until after four months. She became less nervous and jittery and volunteered that she "felt like a new person." A few times she went back to her former high carbohydrate diet and each time she had recurrence of pain and headache after seven to ten days. She lost eight pounds, going from 132 pounds to 124 pounds in the first two weeks on the diet. She then regained 9 pounds in the following four weeks and has remained at 133 pounds right along. At present, after thirteen months, she continues symptom free.

Comment.—The most dramatic feature in this case was the prompt cessation of pain. The headaches ceased after four months although they started to become less severe after two months. This same type of response was observed in Cases 1 and 2; i.e., the pain disappeared much sooner than did the headache.

Although the attacks of abdominal pain and headache are due to the fall in blood sugar, the ingestion of food usually affords relief from pain much sooner than relief from headache. In the case of pain the fall in blood sugar affects the vagal neurons which then stimulate smooth muscle to contract vigorously. The rise in blood sugar following food intake readily reverses this mechanism and pain disappears after several minutes or one-half hour. Pain due to simple hyperperistalsis will dis-

appear sooner than pain due to sustained tetanic contraction. Headache, on the other hand, often persists for hours in spite of recovery from hypoglycemia and suggests that the mechanism responsible for it is not so readily reversed. As mentioned previously, there is probably an escape of fluid through the capillary walls into the brain substance.

CASE 5.—C. S., white female, aged 23 years, single, was admitted to Morrisania Hospital on Sept. 22, 1937, complaining of severe headaches, dizziness, abdominal pain, loss of weight, and attacks of unconsciousness since 1930. She had had usual childhood diseases and an attack of pneumonia at 6 years of age.

In 1930 at the age of 16 years she began to have severe left-sided parietal headaches, which would last several hours, make her quit her work or whatever she was doing and go to bed. Weakness, dizziness, and nausea often accompanied these headaches. Vomiting frequently terminated them. At first the headaches occurred at weekly intervals. After a year they came on two to three times a week. She also had recurrent attacks of epigastric pain, tightness, or soreness, which were often relieved by eating.

The patient lived in a small Pennsylvania town. In 1932 she was admitted to the local general hospital for observation. A workup was negative and she was discharged with a diagnosis of migraine. In 1933 she was employed as secretary in a physician's office. An x-ray examination of the stomach and duodenum showed no abnormality. Because of the persistence of the abdominal pain, appendectomy was advised. This was done but she was not relieved. In 1934 she was admitted to another hospital in Pennsylvania where the only positive finding was a moderate hypertension of 150/100. In February, 1935, she spent three weeks at a leading neurologic clinic in Philadelphia. Repeated neurologic examinations were negative. Special examinations, such as x-rays of the skull, visual fields, and encephalograms, were negative. In 1936 she attended the out-patient department of a New York City hospital, where x-ray examinations were made of the stomach and duodenum and the biliary tract. These were negative. The blood pressure on two occasions was found to be 130/88 and 140/86. A fasting blood sugar was 102 mg. She was given a course of injections of calcium lactate for the migraine, but without relief. During the first six months of 1937 she had three attacks of unconsciousness without convulsions. These lasted about twenty minutes and recovery was spontaneous. She had lost 26 pounds from 1930 to 1937.

She was admitted to Morrisania Hospital on Sept. 22, 1937, and remained there until Nov. 22, 1937, undergoing a most thorough workup. Examination revealed an asthenic, worried, intelligent individual. There were few positive findings. The disks were poorly outlined but not elevated. The retinal veins were engorged, but no hemorrhages or exudates were seen. The blood pressure was 132/80. There was a small area of tenderness without rigidity on deep pressure just to the left of the umbilicus. The following special tests were done and reported as negative: visual fields, vestibular tests, basal metabolism, x-rays of the skull, encephalograms, blood and spinal fluid serologic tests, blood counts, and urinalyses. Three specimens of urine failed to reveal the presence of follicle stimulating hormone. Single blood sugar specimens were reported to be 75, 105, 100, and 90 mg. The patient had headaches about twice a week during her stay in the hospital. These were severe, lasted six to ten hours, and forced her to go to bed. On Oct. 17, 1937, the intern made the following note: "11:50 A.M.: Patient has excruciating headache. In view of previous report of low blood sugar (75 mg.) during episode of headache, 25 c.c. of 50 per cent glucose injected intravenously. Effect to be noted. 1:30 P.M.: Patient is now free of headache and feels fine. At 12:20 P.M., about 20 minutes after glucose was given patient states that her head became 'lighter.'

At 12:30 P.M. she was free of pain. This symptomatic relief warrants consideration of a hypoglycemic state as the cause of these headaches.'' On another occasion the patient was not relieved so readily by glucose. Glucose tolerance test Oct. 26, 1937, revealed: fasting 80; one-half hour, 85; 1 hour, 80; 2 hours, 80; 3 hours, 80, the ''flat'' type of curve. A second test Oct. 29, 1937, revealed: fasting 90; one-half hour, 100; 1 hour, 80; 2 hours, 65; 3 hours, 75; 4 hours, 90. The patient was discharged on Nov. 22, 1937, and returned to her home in Pennsylvania. She was told to stay on a low carbohydrate diet. I have been in touch with her by mail. The abdominal pain, tightness, and soreness have been much milder and she has been free of them for long intervals. The headaches have been just as frequent, although many have lasted for much shorter periods of time. She reports that her appetite is always poor and she is unable to take as much food as the diet calls for. She had no attacks of unconsciousness during 1938. Late in 1939 she had two such seizures.

Comment.—Just why this patient did not respond to the change in diet as did the other four patients is difficult to say. Her headaches were far more severe than those suffered by the others, suggesting that she had a more seriously deranged carbohydrate metabolism. My own experience suggests that patients who give the flat type of curve in the tolerance test respond less readily to the change in diet than do patients with other types of curves. The fact that the blood sugar values in the flat curve are often found to be in the low normal range, i.e., 80 to 90 mg., compared with the fall to marked hypoglycemia, 35 to 50 mg. as observed in other curves, suggests that there are certain unknown factors responsible for the variation in response to the ingestion of glucose. In general, the more severe the hypoglycemia, the better the response to therapy, since it is an easy matter to raise the blood sugar levels in such cases. It appears, then, that in patients with the flat type of curve even on a low carbohydrate diet the liberation of glucose from the liver is greatly inhibited. De Takats and Cuthbert[21] have shown that there is an increase in the storage and fixation of glycogen in the liver after suprarenal denervation and splanchnic section on normal dogs. These workers also suggested that clinically there may occur a block which inhibits the breakdown of liver glycogen. Such a block may conceivably occur in patients in whom the sympathetic nervous system is deficient or in whom the parasympathetic is preponderant.

Dorst[22] has successfully treated with small doses of insulin a group of patients with the flat type of curve. This response to insulin would tend to disprove that such fixation of liver glycogen is due to an excess of endogenous insulin.

DISCUSSION

While only five cases of chronic hypoglycemia are reported in this paper, the ideas and conclusions expressed are based on observations made on a larger number of patients with abdominal pain due to hypoglycemia. These five cases were selected from the group only because

they had undergone laparotomy. Chronic hypoglycemia is a common disorder masquerading as pseudoulcer, chronic appendicitis, abdominal migraine, abdominal angina, effort syndrome, neurocirculatory asthenia, larval hyperthyroidism, etc. The fact that the great majority of patients respond to a low carbohydrate diet suggests that the fundamental cause of the metabolic disturbance is the continued ingestion of a high carbohydrate diet which contains 200 Gm. or more of carbohydrate daily. The diet employed in treatment allows around 100 Gm. of carbohydrate daily. This amount may be increased gradually as long as the patient continues symptom free.

Patients with unrecognized hypoglycemia are often labeled neurotics because no evidence of organic disease is present to account for the abdominal and cerebral symptoms, and because such symptoms often disappear with change in environment, after a heart-to-heart talk with the physician, suggestive therapy, and placebos. Further, such symptoms may be aggravated by, or may recur following, psychic trauma, mental upsets, financial and domestic difficulties. It occurred to me that such unpleasant environmental factors could bring about visceral and mental symptoms by deranging the carbohydrate metabolism. Sudden bad news, for example, could bring on abdominal pain, or even syncope, by causing a sharp fall in the blood sugar. The following observations which I made on patients not included in the cases reported but included in the larger unoperated group illustrate the effect of unpleasant physical and psychic experiences on the blood sugar.

Hypoglycemia and Syncope Following Venipuncture (Fig. 2).—A white male, aged 50 years, reported to the clinic for a glucose tolerance test in the morning after an all-night fast. The patient fell unconscious about three minutes after the venipuncture, was unconscious for two minutes, and recovered spontaneously. The fasting blood sugar was 95 mg. On recovery from syncope, it was 65 mg. It is very likely that the blood sugar had fallen to even lower than 65 mg. and was on the rise when the second specimen was drawn since regain of consciousness must have depended on recovery from hypoglycemia. Such recovery may be attributed to the liberation of adrenalin. The pallor and cold sweat in syncope are evidence of such adrenal-sympathetic activity. I suggest that the syncope was due to the sudden fall in blood sugar precipitated by the unpleasant experience; namely, the venipuncture. Such a sharp fall in blood sugar may result from a cessation in the liver output of glucose mediated by a nervous or humoral mechanism.

Hypoglycemia Following Sudden Bad News (Fig. 3).—A white male, aged 17 years, with a long history of abdominal pain due to hypoglycemia, was suddenly informed that he was to be operated upon the next day. He was obviously upset, appeared pale, and described a feeling of faintness in the precordium and abdomen. He regained composure after several minutes concomitant with a rise in blood sugar. The

fall in blood sugar was not as great or as rapid as in the patient who fainted after venipuncture, but it was of sufficient magnitude to cause moderate visceral discomfort.

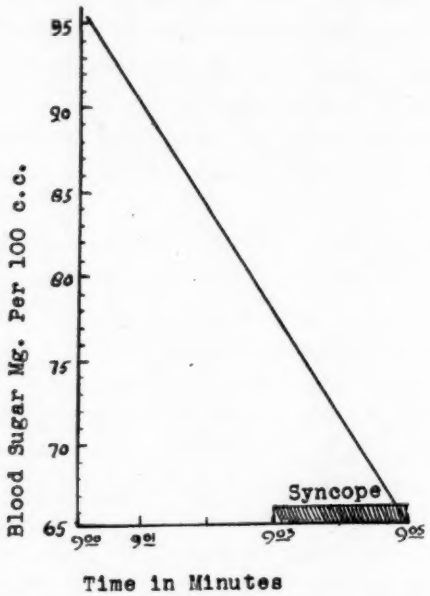

Fig. 2.—Syncope following venipuncture at start of a glucose tolerance test. At 9:00 A.M. fasting blood sugar was drawn. At 9:01 the patient was given 100 Gm. of glucose in 250 c.c. iced water. At 9:02 he appeared pale and nervous. At 9:03 he fell unconscious to the floor. At 9:05 he recovered spontaneously, at which time the second blood specimen was drawn.

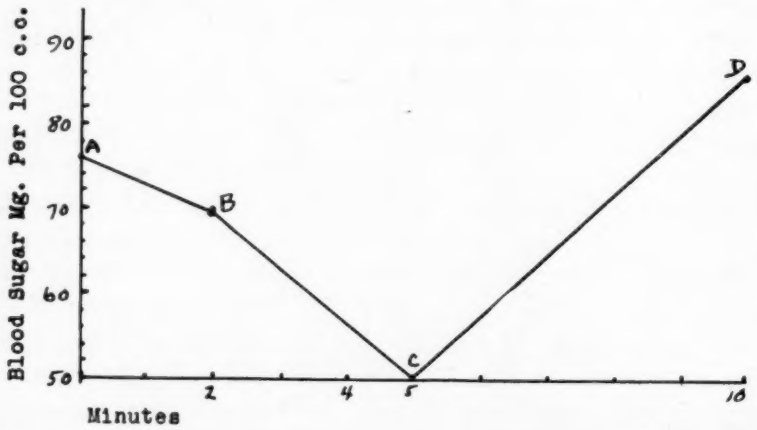

Fig. 3.—At *A* control blood specimen was drawn and subject was told that he was to be operated upon the next day. At *B* blood specimen was drawn and the patient said he had a "weak feeling" in the region of the heart and stomach. At *C* he felt worse, appeared anxious and pale. At *D* patient regained composure and said he felt better.

It has long been known that emotional disturbances may cause hyperglycemia and glycosuria. Such hyperglycemia has been regarded as a defense mechanism in that it increases the amount of glucose available for energy purposes during a period of stress. It is very likely that

immediately following a sudden unpleasant change in environment there is a transient hypoglycemia which is responsible for the unpleasant visceral and mental sensations, such as faintness, abdominal discomfort and pain, nervousness, tremors, pallor, tachycardia, and palpitation, which go to make up what we call fright and fear. Recovery from this phase and efforts made to protect the organism depend on a subsequent hyperglycemia. The individual who faints or who makes no attempt to defend himself probably has no such hyperglycemia.

Through a similar mechanism, chronic psychic trauma may cause chronic symptomatology by derangement of the mechanism controlling carbohydrate metabolism and blood sugar regulation. It is a matter of common knowledge that diabetes is often aggravated by worry or other unpleasant emotional states. This adverse effect is manifest by an increase in the hyperglycemia, signifying that the glucose is not being utilized and is accumulating in the blood. In severe cases the diabetes may become uncontrollable and lead to acidosis and coma. The final common effect, in both diabetics and nondiabetics, of such emotional states will be the same; namely, a decreased glucose and oxygen consumption. Abdominal pain, headache, and dizziness, occurring under such circumstances in both diabetics and nondiabetics, will be due to this final common effect. Thus may be explained the abdominal pain frequently encountered during diabetic acidosis; it is due to the reduced glucose utilization and disappears when such utilization is restored with insulin.

It is thus apparent that the mechanism governing carbohydrate metabolism and blood sugar regulation is a sensitive one and is especially influenced by the emotional state of the patient. Carbohydrate metabolism may thus be unfavorably influenced by a high carbohydrate intake and by psychic trauma. Since it is often difficult to remove the latter, much may be done by dietary management. If, then, a patient presents himself with symptoms obviously due to psychic trauma, he may be relieved of such symptoms by either removing the cause, i.e., the trauma, or by elevation and stabilization of blood sugar levels with a low carbohydrate diet. On such a diet the unfavorable effect on the blood sugar brought on by the psychic trauma is neutralized and symptoms are prevented. We have, therefore, a medium whereby unpleasant emotional states may give rise to a variety of functional symptoms. By depression of blood sugar levels such emotional states may reduce the amount of glucose available for cellular utilization and indirectly reduce the oxygen consumption in the organism. The function of every cell that utilizes glucose as a source of energy will therefore be affected. The severity of the functional disorder will depend on the magnitude of the derangement of the carbohydrate metabolism, and whether or not the changes in cellular function are reversible.

The Relationship Between Fluctuations in Blood Sugar and the Hunger Mechanism.—Normally, after a meal, the blood sugar rises to around 120 mg. in the first hour, 130 mg. in the second hour, 140 mg. in the third hour, and then falls to previous fasting levels, around 80 to 100 mg., during the fourth hour. The only symptom that should occur during the period of decline is the sensation of hunger. The fall in blood sugar stimulates the vagus which in turn causes an increase in gastric motility and tone. Cannon and Washburn[23] showed that "strong contraction of the muscle fibers of the wholly empty stomach, whereby its cavity disappears, makes a part of the sensation which we call hunger." Dickson and Wilson[24] injected insulin into human beings and noted that there was an increase in tone, depth, and rate of peristalsis of the stomach about an hour after the injection, when the blood sugar was around 70 mg. As was shown by Bulatao and Carlson[7] in dogs, and by La Barre and Destree[9] in human beings, gastric motility was replaced by atony when the blood sugar was depressed still further. This explains the loss of hunger and the sensation of epigastric hollowness and emptiness encountered in patients with chronic hypoglycemia where the blood sugar may be maintained for long periods at hypoglycemic levels. Further, in patients who give the flat type of curve in the tolerance test, as an additional cause for the lack of hunger, is the absence of adequate fluctuation in blood sugar levels necessary to stimulate the hunger mechanism.

A most common complaint in individuals after psychic trauma or during periods of worry is loss of hunger sensation. In the neurotic disorder, anorexia nervosa, the glucose tolerance is abnormal and the curves obtained are chiefly of the flat type. Return of hunger, gain in weight, and improvement in mental status, regardless of the therapeutic measures employed, are associated with an improvement in the carbohydrate metabolism. The following is from a recent paper by Ross.[25] He writes, "The conception of anorexia nervosa put forward is that . . . the physiological factor of impaired glucose tolerance with a slowly falling alimentary hyperglycemia leads to a failure of hunger and the impairment of one element of appetite—a normal gastric tonicity. . . . It seems clear, then, that there is a relationship, be it causal or coincident, between the gastric manifestations of hunger and a fall in blood sugar level, and it would be strange if it were merely coincident. If it is causal, then a reasonably rapid fall of alimentary hyperglycemia back to fasting level is necessary for the regular occurrence of hunger; and this fall we know is dependent on a reasonably good glucose tolerance."

One may state that the psychic trauma responsible for anorexia nervosa has disrupted the blood sugar regulatory mechanism which now brings in its wake loss of hunger and a variety of symptoms. Complete removal of the psychic trauma, if this is possible, usually cures the patient. One may say that its removal restores the regulatory mechanism

to its normal status. Where complete removal is impossible, other measures, such as psychotherapy, psychoanalysis, suggestive therapy, hypodermic injections of inert solutions, or time with its ability to make one forget, may cure the patient. These varied therapeutic measures apparently accomplish a final common effect; namely, a restoration to normal of the carbohydrate metabolism.

SUMMARY

Five patients with long histories of recurrent attacks of abdominal pain are reported. In four patients laparotomy failed to disclose organic cause for the pain. Appendectomy was performed in three patients and cholecystectomy in one. A herniorrhaphy was done in the fifth patient. These procedures afforded no relief. In addition to the pain all five patients had nervous manifestations of hypoglycemia which which were not accorded their proper significance. Glucose tolerance tests revealed increased tolerance in all. Low carbohydrate diets afforded relief from pain and other nervous symptoms. Glucose tolerance tests should be done along with x-ray studies in cases of obscure abdominal pain.

The adverse effect of unpleasant emotional states on carbohydrate metabolism is discussed. It is suggested that such a derangement in carbohydrate metabolism may serve as a medium whereby psychic trauma may cause functional disorders.

I wish to thank the following for their cooperation: Dr. Edward P. Flood, Director of Medicine, Morrisania City Hospital, and Dr. Sol Biloon, Dr. W. A. Roberts, and Dr. D. Greenberg, who made available the facilities of their respective wards.

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ACUTE APPENDICITIS IN A SUBURBAN COMMUNITY

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FOR SEVERAL years the mortality figures of acute appendicitis have been of increasing interest to surgeons and public health officials. The importance of the subject is shown by a chart taken from the United States Bureau of Census for 1936, listing conditions which have been selected because of their surgical significance, omitting purely medical conditions.

Much has been done to correct unsatisfactory conditions, but the countrywide mortality in 1936 was 12.8 per 100,000, exactly the same as it was in 1917.[1]

As might be expected, the figures are worse in the rural states due to the "mechanics of isolation" (Krech[3]). Thus, in 1935 the rate in Idaho was 20, in Montana 20.2, in Utah 23.1, while in the same year in New York City the rate was 12.6 and in Philadelphia was 11.

Philadelphia has taken the lead in attempting to control this mortality. Under the chairmanship of J. O. Bower, a Commission on Appendicitis Mortality has worked in collaboration with the Board of Health, the state and county medical societies, the Board of Education, and the Association of Retail Druggists, with gratifying results. Recently, Bower has reported that over a nine-year period the mortality among patients admitteed to twenty-eight Philadelphia hospitals has been reduced nearly 60 per cent.[2] Similar efforts throughout the country would mean a saving of 9,600 lives annually in the United States.

The efforts of the Philadelphia committee have been largely directed towards educating the public in the importance of abdominal pain lasting more than a few hours; the danger of cathartics; and the importance of calling in a physician.

Similar efforts have been made in New York City toward the reduction of mortality from contagious diseases, with the result that, while in 1920 there were 2,876 deaths from measles, whooping cough, scarlet fever, diphtheria, typhoid, and epidemic meningitis, in 1933 the deaths from these diseases had fallen to 629, a reduction of 78 per cent. Yet in the same year the deaths from appendicitis rose from 792 to 1,149, a 45 per cent increase.

In 1935 Krech[3] presented to the New York Academy of Medicine an exhaustive study of acute appendicitis in the years 1921 and 1931 in fourteen of the better New York hospitals. He found a mortality rate of approximately 7 per cent in both years, although there was improvement in earlier hospitalization and in a shorter time elapsing before the patient reached the operating room after admission. It was

Received for publication, April 29, 1940.

interesting to note a marked increase in 1931 in the mortality in the older age groups, perhaps due to the ill effects of unemployment and economic stress.

There have been other similar studies from larger communities, all with much the same figures. Among the more recent of these may be mentioned that of Patterson,[4] reporting 1,211 cases of acute appendicitis from the University Hospital, Iowa City, Ia., from 1919 to 1934, with a 5.2 per cent mortality. In this series there was practically no change in successive five-year periods.

Fig. 1.—Deaths from certain causes in the United States, 1936. (From the U. S. Bureau of the Census, Vital Statistics Report, vol. 5, no. 41.)

Like other writers, Patterson emphasizes the increase in mortality in the later age groups, his series having a mortality of 3.6 per cent in the age group of 11 to 49 years; 16.44 per cent for those over 50 years of age. Hobler,[5] reporting from the Methodist Episcopal Hospital in Brooklyn, N. Y., cites 2,260 cases from 1924 to 1934, with a mortality percentage of 4.3. He quotes Black, who in 1932 reviewed reports from 150 hospitals, totaling 83,144 cases, with an average mortality of 5.5 per cent.

Bancroft,[6] reporting a series from the New York Hospital in 1920, and from the Fifth Avenue Hospital in 1935 to 1936, showed an essentially unchanged mortality rate of 4.3 and 4.2 per cent respectively.

Schullinger,[7] in a very thorough study of the Presbyterian Hospital (New York City) cases from 1916 to 1934, reported an average mortality rate of 5.08 per cent in a total of 2,653 cases, and quotes from various other hospital reports. He felt that there was a slight improvement over this period as a whole.

The most recent reports come from Ravdin and co-workers,[8] who report from Ravdin's service in the Hospital of the University of Pennsylvania. He divides his cases into those previous to and those after 1936, coincident with a change to the consistent use of sulfanilamide in severe cases, especially if there is any peritoneal involvement. In the earlier group he had 8 deaths in 552 cases, a 1.4 per cent mortality, while in the later series there was 1 death in 357 cases, a rate of 0.4 per cent. These figures are the more striking in that acute catarrhal appendicitis is not included.

Arnheim and Neuhof[9] report from Neuhof's service at Mt. Sinai Hospital 212 cases operated upon between 1931 and 1939 with 4 deaths (1.9 per cent).

This report is noteworthy for the absence of a fatal result in 40 consecutive cases of appendicitis with abscess, the average in most other reports running from 5 to 10 per cent. They attribute their good results to a meticulous operating technique, their pre- and postoperative care not differing markedly from that of other authors.

Gile and Bowler[10] reported in 1934 their figures from Hanover, N. H., for a six-year period. Their figures were particularly interesting because they were able to present two groups, one made up of Dartmouth College students living under fairly close control, the other made up of patients within the 75-mile radius served by the hospital. Both groups were cared for in the same hospital by the same surgeons. In the college group there were 110 cases with no deaths. Of these only 1 had gone on to abscess, 1 to diffuse peritonitis. In the general group there were 791 with 17 deaths, a mortality of 2.15 per cent. In this group there were 29 abscesses, 21 cases of diffuse peritonitis. The total figures are 901 with 17 deaths, 1.89 per cent.

Aside from the question of preoperative preparation, operative technique and aftercare, the problem of appendix mortality is chiefly one of education, of the patient or his family in the importance of early medical care and the avoidance of self-medication, and of the physician in early diagnosis and early reference to the hospital.

In discussing the possibilities of improvement, the general tendency is to emphasize early operation and the danger of catharsis. Schullinger perhaps presents the best summary of the factors in the mortality as follows: (1) fears and superstitions of hospitals and operations; (2) cathartics to children for abdominal cramps; (3) purgatives and laxatives prescribed by pharmacists; (4) misinterpretation of ab-

dominal signs and symptoms; (5) medical treatment (morphine, rest, icebag) by local physician; (6) the occasional operator.

While early operation is universally emphasized, it is becoming more clearly recognized that delay of a few hours to correct a depleted fluid balance by infusion is of more value in appropriate cases. Adopting this principle, Beekman[11] has been able to report 136 cases from the children's surgical service of Bellevue Hospital with no deaths.

It is in the late case, with signs of peritonitis not localizing, that the greatest difference of opinion exists. Both immediate operation or Ochsner treatment have their advocates and we believe that Patterson[4] is correct when he says that treatment should be individualized and suit the patient rather than be dogmatic.

It seems that the advocates of Ochsner treatment should emphasize that it is a method that should be carried on in the hospital and under the supervision of the surgeon; otherwise the physician will naturally come to believe that it is a method that can safely be carried out in the home and without surgical aid, a belief that will quickly be reflected in a rising mortality rate.

With the problem in part at least one of public education, and because relatively few studies have been published from smaller communities other than those of individual clinics and surgeons, it has seemed worth while to study the disease as it has occurred in Greenwich, Conn., a suburban community town of 40,000 with almost no factories, a well-trained medical group and a population whose "health sense" has twice won the annual health conservation certificate awarded by the United States Chamber of Commerce.

During the period from June 1, 1933, to Dec. 31, 1939, 525 cases of acute appendicitis have been operated upon at the Greenwich Hospital. Interval operations and appendices removed in the course of operation for other primary diseases have not been included. No case has been included unless the pathologic report substantiated the diagnosis, with the exception of those in which an abscess was drained but the appendix not removed.

TABLE I

AGE GROUPS AND RELATION TO MORTALITY

			DEATHS
To 10 yr.	61 (11.6%)		
10-20 yr.	192 (36.5%)	449 cases (mortality 0.2%)	1
20-30 yr.	130 (24.7%)		
30-40 yr.	66 (12.5%)		
40-50 yr.	40 (7. 6%)		2
50-60 yr.	20 (3. 8%)	75 cases (mortality 8.0%)	2
60-70 yr.	14 (2. 6%)		2
70-80 yr.	1 (0.19%)		
Not noted	1		

This emphasizes, as do all published reports, that acute appendicitis is a disease of young adult life and that the mortality is greater in the later decades. Sprague[12] reports a mortality rate of 1.5 per cent in 81.5 per cent of 1,463 cases from the Newark City Hospital between the ages of 10 and 40 years, but a 13.9 per cent mortality in the group from 40 to 80 years of age.

TABLE II

DURATION OF ATTACK AND RELATION TO MORTALITY

			DEATHS
To 12 hr.	175 (33.5%)		
12-24 hr.	194 (36.9%)	465 (mortality 0.8%)	
24-48 hr.	96 (18.2%)		1
48-72 hr.	22 (4.4%)		3
72-	32 (6.0%)	54 (mortality 11.0%)	2
Not noted	6 (1.2%)		1

These figures are in line with others and emphasize the remark of Ashurst:[13] "There is no problem in acute appendicitis—the problems of appendicitis are the problems of its complications."

History.—One hundred and fifty-four patients had had previous attacks.

The present attack as described in the records was typical in 505, atypical in 16, and not noted in 4. The first symptom was pain in 507 cases, nausea and vomiting in 9, diarrhea in 9.

TABLE III

CATHARSIS

Taken by 181 patients			
No record	97	Ordered by family	52
None taken	247	Ordered by self	84
Oil	30	Ordered by physician	10
Salts	52	Ordered by druggist	2
Other	56	No note	33
Enema	79		

Catharsis is usually noted as one of the causes of increased mortality, but its true importance is not yet determined. Catharsis is the one detail which is most likely to be omitted in the intern's history. Thus, Krech found no mention of catharsis in 69 per cent of the 1921 charts,

TABLE IV

RELATION OF CATHARTICS TO PREOPERATIVE DELAY

ENTIRE SERIES (525)			PATIENTS TAKING CATHARTICS (181)	
To 12 hr.	175 (33.5%)		39 (21.5%)	
12-24 hr.	194 (36.9%)	88.6%	75 (41.4%)	83.8%
24-48 hr.	96 (18.2%)		38 (20.9%)	
48-72 hr.	22 (4.4%)		7 (3.8%)	
72- hr.	32 (6.0%)		22 (12.1%)	
Not noted	6 (1.2%)			

63 per cent of the 1931, while information was incomplete in 20 and 16 per cent, respectively.

While our figures represent a relatively small total, they are presented for what they are worth, and in part because we were surprised at the apparently slight effect of catharsis on delay in operation and on the extent of appendical involvement.

It may be that Nature protects the patient from the effects of unwise catharsis by rejecting it.

On the other hand, Bower[14] in reporting from 1928 to 1930 from Philadelphia makes the statement that when: no cathartic was given in the acute attack, 1 in 80 died; one cathartic was given in the acute attack, 1 in 13 died; two or more catharties were given in the acute attack, 1 in 7 died.

It is our impression that catharties may be more important as a cause of delay than in the actual local damage that they cause.

TABLE V

RELATION OF CATHARSIS TO PATHOLOGIC STATE OF APPENDIX

	ENTIRE SERIES (525)		PATIENTS TAKING CATHARSIS (181)	
Without peritonitis				
Acute catarrhal	70 (13.3%)		21 (11.6%)	
Suppurative	247 (47.0%)	75.3%	72 (39.7%)	77.8%
Gangrenous	79 (15.0%)		48 (26.5%)	
Abscess	37 (7.0%)		12 (6.0%)	
Local peritonitis				
Suppurative and gangrenous	56 (10.6%)		15 (8.2%)	
Diffuse peritonitis				
Suppurative and gangrenous	29 (5.5%)		10 (5.5%)	
Not noted	7 (1.3%)		3 (1.6%)	

Diagnosis.—This was correct in 506 cases. In 12 the preoperative diagnosis could not be determined from the chart. The incorrect diagnoses were: perforated ulcer, 3; acute cholecystitis, 1; acute pancreatitis, 1; ovarian cyst with twisted pedicle, 1; abscess of abdominal wall, 1.

TABLE VI

INCISION		DRAINAGE	
No record	40	Peritoneal cavity	122
McBurney	347	Abdominal wall	20
Split rectus	42	Abscess, appendix not removed	3
Retracted rectus	94		
Midline	1		
Pfannenstiel	1		

We prefer the McBurney incision unless the diagnosis is questionable, feeling that it gives adequate exposure with minimum risk of peritoneal contamination and that drainage through this incision, if necessary, is satisfactory and least likely to be followed by hernia.

Drainage follows the usual rules and is usually established by a soft cigarette drain.

Pathology.—As one would expect, in view of the large number of early operations, the changes in 75 per cent of the cases were confined to the appendix.

The differentiation between local and diffuse peritonitis is difficult to be sure of, the interpretations of the individual surgeons probably varying considerably. Where the diagnosis as written did not check with the operative description, we have classified the case according to the latter.

TABLE VII

ANESTHESIA		PRELIMINARY MEDICATION	
Avertin base followed by G-O-E	431	Morphine and atropine	240
G-O-E	86	Atropine	210
Spinal	1	Morphine	19
Drop ether	5	Codeine	2
No record	2	Nothing	52
		No record	2

Obviously we are well satisfied with avertin as a basic anesthetic. We have not found the difficulties and danger in its use reported by Beecher[15] from the Massachusetts General Hospital where its use has been discontinued. In fairness it should be stated that we have an adequate and well-trained anesthetic and nursing staff, which we believe to be important when this anesthetic is used. The senior author, for instance, finds it a much less practical anesthetic on his service at Bellevue Hospital, where it is more difficult to give special attention to a patient when coming out of anesthesia.

The amount of preliminary medication has been somewhat of a surprise. While we have had no difficulties following the use of morphine and avertin, we feel that morphine as a preliminary is probably bad practice and should be abandoned as routine. This opinion is based on the emphatic statements of many of the more experienced anesthetists.

TABLE VIII*

POSTOPERATIVE COMPLICATIONS (525 CASES)

Wound		
	Deep infection	16
	Hematoma	7
	Disruption	1
	Secondary pelvic abscess	1
Pulmonary		
	Pneumonia	7
	Embolus	3
	Bronchitis	2
Gastrointestinal		
	Fistula	2

*Figures of superficial infections, stitch abscesses, etc., are too incomplete to be of any value and are omitted.

Mortality.—There have been 7 deaths in this series, 1.3 per cent. As shown in Tables 1 and 2, deaths occur chiefly in the older age groups and in the late cases.

There were no deaths in the 396 cases in which the disease was limited to the appendix nor in the 37 cases of abscess.

One patient with local peritonitis (pelvic) died, a mortality rate in this group of 1.8 per cent.

Of 29 patients described as having diffuse peritonitis, 6 died (20.6 per cent).

Four of these 7 had been sick less than forty-eight hours. One was a patient who at operation had a *B. coli* pelvic peritonitis. She showed no resistance, dying eight days following operation with the signs of a spreading peritonitis.

The 6 who had diffuse peritonitis at operation were aged 36, 44, 48, 59, 66, and 68 years. They had been sick for 22, 30, 36, 36, 56, and 96 hours before operation. Three had had saline cathartics; two, irrigations before admission. There was no note as to catharsis on the remaining charts.

At operation all had gross leakage from ruptured appendices. *B. coli* were reported in all cultures.

Aside from the possible effect of catharsis, vigorous treatment by a physiotherapist may have been a factor in the rupture of one of these appendices.

In another case pain developed a few hours after eating clams which had been dug in a prohibited area, and this together with atypical signs led to delay in operating until peritonitis was well established.

There were two errors in diagnosis. In one case a previous history of ulcer and fulminating signs led to a diagnosis of perforated ulcer, an error which had no influence on the ultimate result. In the other what was thought to be a gangrenous gall bladder was removed and only after its removal was a gangrenous appendix recognized. In this case an unnecessary procedure prolonged the operation and probably was a factor in the patient's death.

SUMMARY

A partial review of recent literature covering the mortality figures of acute appendicitis is presented. The figures from a suburban community of 40,000 population, with a high average intelligence and "health sense," as well as a well-educated medical group, are discussed.

Even in a community of this sort, over 10 per cent of all cases were operated upon after a delay of over forty-eight hours. It is in the education of the public and the medical profession toward the further diminution of this figure that lies our best hope of further cutting down the mortality.

The mortality from acute appendicitis in this community over a seven-year period is 1.3 per cent.

Catharsis does not seem to be an important factor in the mortality rate in this series.

The use of sulfanilamide, especially in cases with peritoneal involvement, offers hope of improvement.

Study of the fatal cases emphasizes that overwhelming peritonitis may be established early and the importance of early recognition of the case with atypical symptoms and signs.

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LIVER INJURIES WITH A CASE REPORT OF REPEATED HEMORRHAGES THROUGH THE BILIARY DUCTS

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THE symptoms of the usual liver injury include pain that may be severe and localized over an area in the liver or in the region of the blow, such as would be found in a lateral chest contusion. This type of injury may cause widespread pain similar to pleuritis.[1] Localized pain may be absent, but a liver injury should be kept in mind if there has been a blow or contusion anywhere near the region of the liver. Rigidity, shock, signs of internal hemorrhage or bile irritation of the peritoneum indicate an emergency, but these findings are often not pronounced enough to warrant opening the abdomen at once. Repeated blood counts will aid in differentiating hemorrhagic from traumatic shock. The apparently mild upper abdominal injury must be watched closely. Quick recovery from the immediate shock may be followed by delayed massive hemorrhage.

The right lobe, due to its anatomical position, is the most frequently affected. Any area may be involved and deep wounds by contrecoup may occur. Deep wounds may not show any external evidence of capsular tear and, as in the case to be presented, may bleed profusely through the bile ducts. Multiple tears and deep hematomas that are often followed by abscess formation are found at operation or autopsy.

Hematomas are aspirated and those that later go on to abscess formation are drained in the usual manner, but the technique of peritonization of the area to be drained as advised by Robertson[2] is probably the safest procedure.

A liver wound should be loosely packed because tight packing may cause necrosis. The gauze is allowed to remain in place for one week. In Krieg's forty-one cases that were treated by packing, the gauze was not inserted into the wound with enough pressure to control the bleeding and frequently it was merely placed against the wound. When large amounts of gauze were used there developed symptoms of obstruction.[3] Drainage is necessary because collections of blood, bile, or pus may occur. Closure of the wound by mattress sutures is a method that is preferred by many surgeons and, if this procedure is followed, drainage should be inserted into the depth of the wound in order to prevent the formation of an intrahepatic hematoma and to take care of the bile leakage from torn biliary ducts.

Case Report.—(No. 21464, American Hospital for Diseases of the Stomach.) This was an unusual case of injury to the liver without rupture of the capsule and

Received for publication, April 29, 1940.

intraperitoneal bleeding but followed by repeated massive hemorrhages through the biliary ducts. The clinical picture and surgical treatment were therefore quite different from those just described.

A truck tire rim blew off, striking the anterolateral chest wall, upper abdomen, and face. The man was admitted to another hospital on June 6, 1933, where he was given immediate treatment for shock, fractured seventh and eighth ribs, and fractured nose. The injury to the thoracic cage masked the intraabdominal injury so that it was not recognized at this time in spite of hematemesis on two occasions and tarry stools that were noticed by the patient. After seven weeks of hospitalization he was discharged and returned to work nine weeks after the date of injury. Two weeks later while at work he felt a sudden sense of suffocation with severe pain in the upper abdomen but most marked in the gall bladder area. He vomited a large amount of blood and there was gross blood in the stool.

When admitted to our service on Sept. 17, 1933, he stated that he had vomited a large amount of blood that morning and gross evidence of blood was found in the stool.

The patient was a very powerful man and the general physical condition was surprisingly good in spite of all the bleeding that had reduced the red cells to 2,790,000 and the hemoglobin to 47 per cent.

All physical findings were negative but no gastrointestinal x-rays were attempted due to the continued bleeding. Nothing was given by mouth for three weeks and by the use of blood transfusions and intravenous glucose he improved to the extent that the red cell count was 4,190,000 and hemoglobin 70 per cent. During this time, however, he vomited on three occasions a very thick black material that on examination proved to be a mixture of blood and bile. The stool finally was negative and after three weeks of withholding fluids by mouth, a liquid diet was allowed. The stool only remained negative for occult blood for two days and then traces appeared again. However, for psychological reasons an increase in diet was allowed and no increase in the bleeding occurred. For the same reason the patient was allowed to go home two months after admission, still showing a trace of occult blood in the stool, but was to return for a complete gastrointestinal x-ray.

He was readmitted to the hospital three weeks later and plainly showed the effects of a severe hemorrhage the night before. During the three weeks at home he had several attacks, consisting of a sense of tightness in the liver area and severe colicky pain followed by nausea and vomiting of the same thick black material that had been examined in the hospital. He also passed this same type of material by bowel.

Five days later the blood transfusions and intravenous glucose injections had caused sufficient improvement to warrant an x-ray examination of the stomach and duodenum. A large defect in the pyloric end of the stomach was demonstrated, but the roentgenologist was unable to state whether this was due to adhesions or ulcer.

After two more days of blood transfusions and intravenous glucose injections an upper right rectus incision revealed a mass of adhesions over the gall bladder and duodenal areas. No ulcer was demonstrable, but in view of the large amount of hematemesis it was deemed advisable to open the duodenum. The usual Heineke-Mikulicz incision was made. No definite ulcerated areas were found, but several small congested areas in the mucosa were touched with the cautery and the incision was closed transversely. This did not explain the bleeding and, on releasing the dense adhesions, the gall bladder was found to be very dark in color, to be enlarged, and to contain a smooth hard mass the size of an egg. The gall bladder was removed and the bile ducts were explored through the patulous cystic duct. Some very dark material of the same type that he had vomited was found, but there was no

evidence of tear of the ducts or liver. The large mass in the gall bladder proved to be inspissated blood and bile.

He made an uneventful postoperative recovery and was discharged on the sixteenth day. The stool was negative for occult blood.

One week later he had another attack of colicky pain in the subhepatic area lasting one hour and vomited a small amount of the very dark material that had been observed on previous occasions. A large amount of green black fluid was passed by bowel. There followed a number of these short attacks at intervals of a few days. During the last attack a branching clot that appeared to be a cast of the hepatic ducts was vomited. This proved on examination to be inspissated blood and bile. Since then he has been entirely free of all the former symptoms and at present is in excellent health.

It is very evident that the operative procedure did not contribute to the final cure, but it is interesting to note that this case was in all probability a cavity and hematoma deep in the substance of the liver that continued to necrose and bleed through a large biliary duct until healing finally occurred. There is no other explanation that we can give for the continued bleeding through the biliary channels.

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THE ORAL ADMINISTRATION OF SYNTHETIC VITAMIN K (2-METHYL-1, 4-NAPHTHOQUINONE)

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SINCE the discovery of the relationship of hemorrhagic tendencies to vitamin K deficiency in 1929[1] and later in 1935[2] by Dam, there have been many reports corroborating his results and presenting further observations upon the source, extraction, assay, and clinical application of this vitamin. Some of the leaders in this experimental work have been referred to in a recent report by Doisy and his associates,[3] who have been responsible for the synthesis of vitamin K in their laboratory. They found that the synthetic compound was 2-methyl-1, 4-naphthoquinone. To support this contention, Almquist and Klose[4] and Fieser,[5] independently following different analytical procedures, arrived at the same structural formula. This compound was an oil-soluble active substance whose action was thought to be either through the phenol or quinone radicals. Since the substance could not be used parenterally except in a large volume of solvent, experiments were conducted to discover an active compound with greater solubility, and such a compound was found by Doisy and coworkers[6] to be 4-amino-2- methyl-1-naphthol hydrochloride.

Clinical application of vitamin K has been discussed and reviewed by Rhoads,[8] Snell,[9] Stewart and Rourke,[11] and others. Therefore, reference is made to their reports of original investigations regarding vitamin K and the natural substances rich in this vitamin. Before the synthesis of an active compound, the prime sources were alfalfa and putrified fish meal. Green leaves, vegetables, dried chestnuts, spinach, peas, and egg yolks also contained the active substance.

Vitamin K was intimately associated with the plasma prothrombin which was involved in the mechanism of the clotting of blood. Experimentally, a prolongation of the prothrombin time was produced in a chick by withdrawal of the vitamin in the diet. This could not be produced in other common laboratory animals. Hawkins and Brinkhous[12] produced a prothrombin deficiency in a dog with a biliary fistula, but it took several months to develop. Smith, Warner, and

Received for publication, May 3, 1940.

Brinkhous[13] produced a marked hypoprothrombinemia in twelve hours by chloroform anesthesia, and a similar condition by administering phosphorus and carbon tetrachloride. These observations indicated that liver damage was responsible for the reduction of plasma prothrombin. This finding was supported by Warner,[14] who produced a marked prothrombin deficiency by partial hepatectomy. In six dogs Andrus and his associates[15] performed complete hepatectomies. They found a continuous decided fall in prothrombin concentration after hepatectomies and held this as evidence that the liver under normal conditions was responsible for the formation of prothrombin. As further proof, Andrus and associates instilled vitamin K into the duodenum and failed to alter the typical decreasing curve of the plasma prothrombin fall after hepatectomies. These experiments seemed to indicate that the liver was the chief, if not the only, source of prothrombin.

Clinically, liver damage might take place in various diseases, and thus hypoprothrombinemia might occur and predispose the patient to hemorrhagic tendencies. Any obstruction to the extrabiliary passages might secondarily cause damage to the liver. Primary liver disease through infections, neoplasms, metabolic or other factors might affect the parenchyma of the liver to such an extent as to produce a lowered plasma prothrombin level. Thus, if the "factory" were not functioning properly, one might expect that any efforts made to maintain a normal prothrombin level through synthesis by the liver would be futile.

Through any of the preceding factors an individual might develop a deficiency in bile salts because there was inadequate manufacture by the liver or because there was a "block" to the outlet of bile salts into the intestinal tract. Since vitamin K is a fat-soluble substance, its absorption depends upon the presence of bile salts in the intestinal tract. In addition, there might be insufficient absorption from the gastrointestinal tract, as in intestinal obstruction or ulcerative colitis. If there is obstruction to the flow of bile from the liver, there is presumably an inhibition of production of bile salts by the liver. If this obstruction is liberated, as through surgical intervention, a sudden release of stagnant bile occurs. Walters and others[18] have analyzed bile in such cases and found that the total bile-acids secretion might be definitely lowered. This accounts then for the inability of the body to utilize fully vitamin K in obstructive jaundice without the addition of normal bile salts even after the obstruction has been released. This phenomenon, however, is largely dependent on the presence of a damaged liver.

The prothrombin determinations in our series were done by the method of Smith* and associates[10] because their "bedside" test had such practicability. In a comparison between the Smith and the Quick tests we found that the variation was slight with the exception of extremely low levels where the Quick test was more sensitive. For clinical use the percentage of error was within practical range. The values obtained were recorded in the percentage of normal; that is, the percentage of the prothrombin clotting activity of a normal individual. Determinations were done daily in most instances. Coagulation times by the capillary tube method were done in some of the patients, but no delay was noted except in two or three instances when the prothrombin clotting time was markedly prolonged.

This paper deals only with oral administration of vitamin K.† Several patients have been given a soluble vitamin K for parenteral use, but at present our series is too small to include in this report. However, the synthetic vitamin K for intravenous administration is active and promises to be about as effective as the insoluble type.

Seventy-five patients who had biliary tract surgery, or who were suspected of having a prolonged prothrombin time, were tested. Determinations were made daily; the prothrombin percentage recorded was the lowest reading obtained in each case. Eighteen patients treated were jaundiced (Table I). The prothrombin clotting activity reached normal levels in each instance. Rhoads and Fliegelman[16] and Macfie with his associates[17] have recently reported a good response with the synthetic vitamin in jaundiced patients. It is seen in Table I that there is little correlation between the degree of jaundice, or its duration, and the hypoprothrombinemia. Five patients (Table II) with a reduced prothrombin clotting activity, but not jaundiced, were also treated. The percentage of activity returned to normal in all except one case, a patient in terminal condition resulting from a carcinoma of the rectum.

*Method of plasma prothrombin determination:

Source of Thromboplastin.—Rabbit brains or lungs are macerated in a mortar. Salt solution, 0.9 per cent, is then added. The material is allowed to stand in the icebox for three hours. The supernatant fluid is decanted and strained through gauze. Usually the solution is centrifuged. The thromboplastin, which is present in the filtrate, is kept in the icebox. It is best to warm the sample of thromboplastin to room temperature before using. The activity of the thromboplastin decreases daily; thus a normal prothrombin time for the sample of thromboplastin used must be made daily.

Method of Prothrombin Determination.—A stop watch is used for accuracy in timing the clotting time. One-tenth cubic centimeter thromboplastin is placed into a small serologic tube. To this is added 0.7 c.c. of blood drawn quickly and atraumatically. The time is recorded in seconds from the time the blood contacts the thromboplastin to the time the clot appears in the tube. The tube is slowly inverted until clotting occurs. A normal patient is tested and checked several times to get the correct normal prothrombin time.

$$\frac{\text{Normal plasma prothrombin time in seconds}}{\text{Patient's plasma prothrombin time in seconds}} = \text{percentage of normal clotting activity.}$$

A prolonged prothrombin time in seconds will give a low percentage of clotting activity.

Bleeding Levels.—Bleeding may occur at any level below 70 per cent; however, it is relatively uncommon until the level has approached 50 per cent.

†The vitamin K and bile salts used in this report were kindly furnished by Eli Lilly and Co., Indianapolis, and Parke, Davis and Co., Detroit.

TABLE I

JAUNDICED PATIENTS WITH REDUCED PROTHROMBIN CLOTTING ACTIVITY WHO RECEIVED VITAMIN K

CASE	DIAGNOSIS	JAUNDICE		INITIAL PRO-THROMBIN	AFTER VITAMIN K
		DURATION	DEGREE*		
1. A. B.	Carcinoma of pancreas	2 mo.	4	64%	100%
2. P. A.	Carcinoma of pancreas	1 mo.	4	75%	100%
3. S. V.	Common duct stone	6 wk.	3	37%	100%
4. P. L.	Carcinoma of pancreas	3 mo.	3	48%	100%
5. M. Mc.	Carcinoma of pancreas	3 wk.	3	71%	100%
6. P. V.	Common duct stone	4 wk.	2	64%	100%
7. H. M.	Common duct stone	3 wk.	2	64%	91%
8. M. E.	Acute cholecystitis	10 days	2	67%	100%
9. J. P.	Cirrhosis of liver	1 mo.	2	69%	100%
10. H. M.	Acute cholecystitis	1 wk.	2	70%	96%
11. L. T.	Common duct stone	6 wk.	2	76%	100%
12. T. F.	Carcinoma of pancreas	6 wk.	2	76%	100%
13. M. M.	Cirrhosis of liver	2 mo.	2	77%	100%
14. F. G.	Cirrhosis of liver	1 mo.	2	79%	100%
15. M. R.	Common duct stone	4 wk.	2	79%	100%
16. J. A.	Common duct stone	2 wk.	1	54%	100%
17. M. H.	Common duct stone	2 wk.	1	62%	94%
18. D. W.	Cirrhosis of liver	3 wk.	1	74%	91%

*Degree of jaundice: *1*, slight; *2*, moderate; *3*, severe; *4*, very severe.

The initial dose arrived at after our experimentation was 6 mg. of vitamin K and 2 Gm. of bile salts. As a routine, 0.33 Gm. (5 gr. capsule) of bile salts was given with each milligram of vitamin K. A daily dose of 2 to 6 mg. maintains a normal prothrombin level in most patients. The maintenance dose was determined and must be checked by daily prothrombin determinations. Our observations seemed to indicate that all low prothrombin levels can be returned to normal with an initial dose of 6 mg. and can be held with a maintenance dose of 6 mg. daily. In many patients the prothrombin time can be maintained at a normal level on a much smaller dosage.

TABLE II

NONJAUNDICED PATIENTS WITH REDUCED PROTHROMBIN CLOTTING ACTIVITY WHO RECEIVED VITAMIN K

CASE	DIAGNOSIS	INITIAL PROTHROMBIN	AFTER VITAMIN K
1. A. K.	Biliary fistula	57%	100%
2. O. P.	Intestinal obstruction	68%	100%
3. S. K.	Subphrenic abscess	67%	100%
4. C. A.	Carcinoma of rectum	69%	74%
5. E. C.	Nephritis	69% (bleeding)	98%

The following case illustrates the effect of the therapy:

Case M. R. (Fig. 1) presented a moderate degree of jaundice of four weeks' duration due to a common duct stone. Preoperatively, the prothrombin activity was 61 per cent. This patient was given 1 mg. of vitamin K three times daily, with 0.33 Gm. of bile salts to each milligram. After one dose the level in twenty-four hours was 74 per cent. In forty-eight hours after three doses the level reached 91 per cent. Such

a gradual rise in the plasma prothrombin was obtained with small doses. The level dropped to 75 per cent in twenty-four hours. Then, an initial 6 mg. dose of vitamin K and 2 Gm. of bile salts were given. A rise to 95 per cent was then attained in one-half hour. Other patients responded similarly to these doses. There is no objection to the use of small doses of the compound when preparing a patient for surgery; however, if an immediate effect is sought, an initial large dose is recommended.

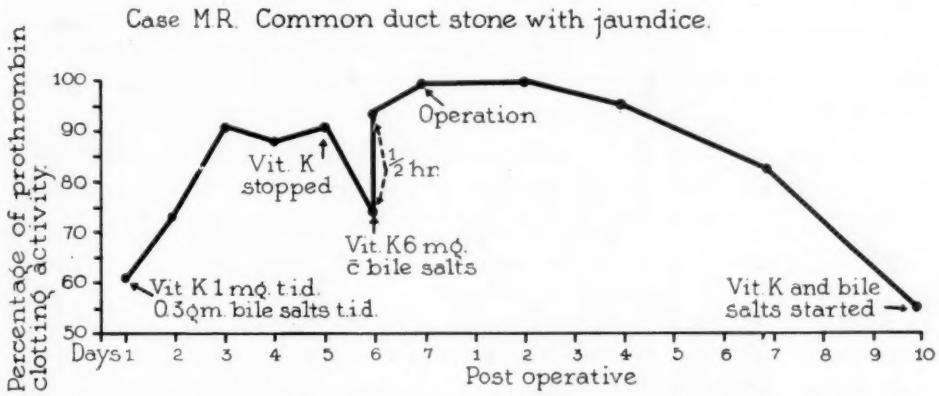
Case M.R. Common duct stone with jaundice.
Percentage of prothrombin clotting activity
100
90
80
70
60
50
Operation
Vit. K stopped
½ hr.
Vit. K 6 mg. c bile salts
Vit. K 1 mg. t.i.d. 0.3 gm. bile salts t.i.d.
Vit. K and bile salts started
Days 1 2 3 4 5 6 7 1 2 3 4 5 6 7 8 9 10
Post operative

Fig. 1.—On a dosage of 1 mg. of vitamin K t.i.d. the prothrombin activity gradually rose to normal, then dropped as soon as the treatment was discontinued. On a single dose of 6 mg. the prothrombin activity rose sharply to normal in one-half hour. A choledochostomy was performed on the following day. Treatment was again discontinued. A gradual reduction in prothrombin activity recurred, reaching a low level on the tenth day.

Vitamin K must be given with bile salts when the latter are not secreted into the intestinal tract. We found that in the absence of bile salts the response was negligible. This was illustrated by the case of A. K. (Fig. 2); the patient gave a good response to an initial dose of 6 mg. of vitamin K with bile salts, rising from a 57 per cent level to 100 per cent. However, after the prothrombin time had dropped in twenty-four hours to 47 per cent, 6 mg. of the vitamin were given without bile salts, but there was no response. Then 1 mg. of the compound was given with 0.33 Gm. of bile salts, three times daily. After one dose, the level was 63 per cent. After four doses, the level was 100 per cent. Another patient, O. P. (Fig. 3), was treated for acute intestinal obstruction by Wangensteen gastric siphonage for seven days. A vitamin K deficiency was present due to starvation. We assumed that bile salts were secreted into the intestinal tract. Three milligrams of vitamin K were given without bile salts. The duodenal tube was clamped off for two hours. The level rose from 79 to 91 per cent in twenty-four hours. The next day it dropped to 70 per cent. Six milligrams of vitamin K, without bile salts, were given and in one-half hour the level was 90 per cent. In twenty-four hours it was again 90 per cent, and in forty-eight hours it was 100 per cent. Thus, one is guided by the etiologic factor of the vitamin K deficiency as to whether or not bile salts should be given in conjunction with vitamin K.

The response to the synthetic vitamin K is apparently immediate. We found that, when an adequate dose was given, a rise in the prothrombin level was obtained within one hour. Five patients were observed to determine the rapidity of action of the compound. In the

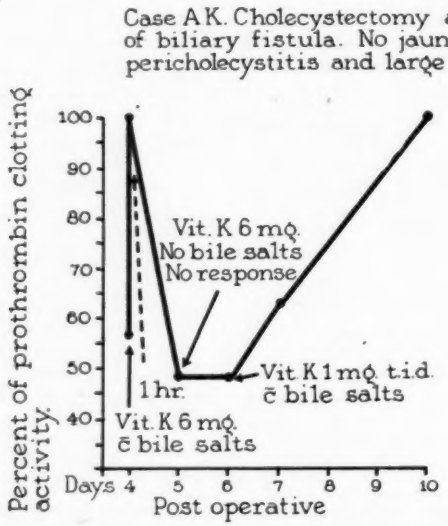
Case A K. Cholecystectomy and removal of biliary fistula. No jaundice. Marked pericholecystitis and large liver.
Percent of prothrombin clotting activity
100
90
80
70
60
50
40
Vit. K 6 mg. No bile salts No response
Vit. K 1 mg. t.i.d. c bile salts
1 hr.
Vit. K 6 mg. c bile salts
Days 4 5 6 7 8 9 10
Post operative

Fig. 2.—The prothrombin activity rose to normal one hour after a dose of 6 mg. of vitamin K and 2 Gm. of bile salts. The subsequent drop to the original low level within twenty-four hours was characteristic of patients with damaged livers. A second dose of 6 mg. of vitamin K, without bile salts, had no effect. A smaller dose of 1 mg. of vitamin K t.i.d., given with bile salts, produced a gradual rise to normal.

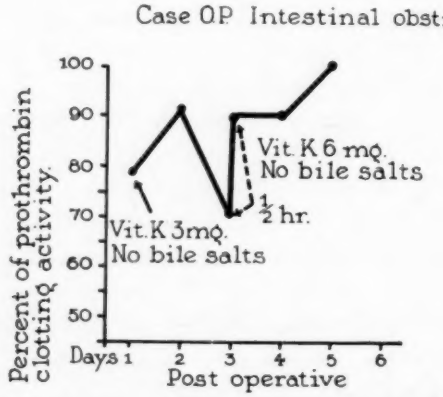

Fig. 3.—A reduction in prothrombin activity due to intestinal obstruction promptly returned to normal using vitamin K alone.

case of A. K. (Fig. 2), one hour after an initial large dose, the level rose from 57 to 100 per cent. In the case of M. R. (Fig. 1), a 75 per cent prothrombin activity increased to normal one-half hour after an initial 6 mg. dose. In three other cases there was a similar rise in one-half hour from 70 to 90 per cent, 66 to 80 per cent, and 74 to 90 per cent, respectively. Absorption of vitamin K is presumed to take place in the jejunum. The effect was so rapid that one might even

suspect absorption from the stomach. Since the absorption was so fast, we gave the vitamin to several patients who were being treated by constant gastric siphonage. The vitamin K was given by mouth, the duodenal tube clamped off for an hour, and the prothrombin level determined. The response was good in all cases.

An attempt was made to determine the duration of the effect of a single dose of the vitamin. The rise in prothrombin activity following a single dose was maintained in some cases for only twelve hours; in others, for three days; and in some it remained normal. We thought that clinically the patients with severe liver damage did not maintain the prothrombin level so well as did those with relatively good liver function. Undoubtedly there were exceptions to this. With such a variation in the maintenance of the plasma prothrombin one can be assured that the level is kept within normal limits only by repeated prothrombin determinations. Maintenance doses of 2 mg. of the vitamin, three times daily, are recommended if one is unable to perform the test very often. In the case of M. R. (Fig. 1) it was seen that the preoperative level of 75 per cent was increased to 100 per cent by a single 6 mg. dose. There was no abnormal bleeding. Not until the eighth postoperative day did the level begin to drop. On the tenth day it had reached 55 per cent. At this point therapy, to which the patient responded immediately, was started. This patient maintained a normal level for eight days postoperatively after only a single initial large dose of the compound.

A normal prothrombin activity before surgery does not indicate that the prothrombin percentage may not drop to dangerously low levels postoperatively. The fourth to the seventh day after operation was found to be the time when levels were lowest. Fig. 4 shows the postoperative prothrombin level in seven cases following biliary surgery. Five of these patients were jaundiced; two were not jaundiced. In all of them there was a significant drop in prothrombin activity between the fourth and seventh days, an interval that might be called the "critical period." Patient P. V. (Fig. 5) had a moderate degree of jaundice of four weeks' duration, due to a common duct stone. This patient was given daily doses of 3 mg. of vitamin K with bile salts preoperatively. On the fourth postoperative day the level dropped to 63 per cent. Six milligrams of the vitamin, with bile salts, were given, and in one-half hour the level was 100 per cent. This level was then maintained on a 3 mg. daily dose until the patient was on an adequate diet. A similar postoperative course was illustrated in the case of M. R. (Fig. 1).

We observed no toxic effects and no nausea or vomiting after the administration of the synthetic vitamin K. In this respect the synthetic vitamin K is far superior to the extracts which frequently caused

nausea and vomiting. One patient was given as much as 50 mg. of the compound in a twenty-four-hour period without any ill effects. However, the prothrombin level could not be elevated above normal even with this relatively massive dose. From this observation we supposed that there was a stabilizing effect, most likely through the liver, which prevents an increase in the plasma prothrombin level above normal.

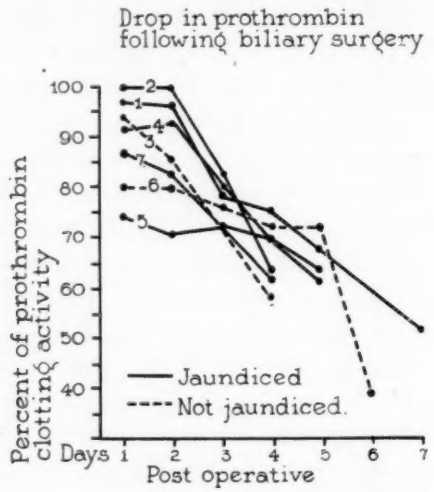

Fig. 4.—Following biliary surgery in both jaundiced and nonjaundiced patients, there was a significant drop in prothrombin levels between the fourth and seventh days.

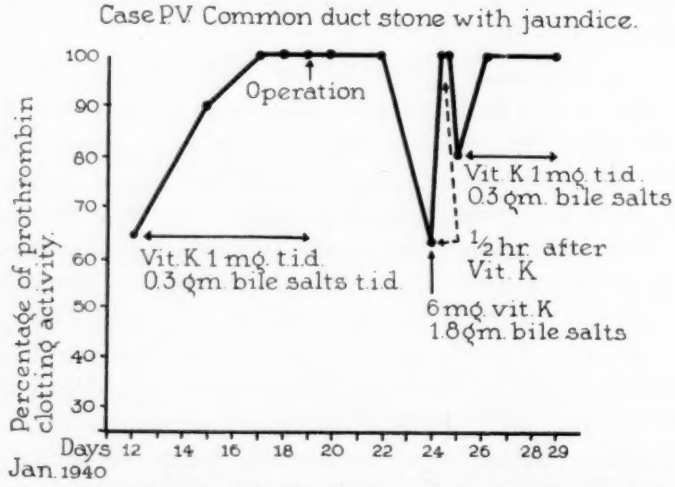

Fig. 5.—A normal prothrombin level was obtained by the preoperative administration of 1 mg. of vitamin K and 0.3 Gm. of bile salts t.i.d. The level dropped abruptly four days postoperatively. After a large dose of the drug, the prothrombin activity rose to normal in one-half hour. Subsequent daily administration was necessary to maintain the normal level.

In only one patient (Case M. M., Table I) did we find active bleeding (epistaxis and from the gums) as the result of jaundice. He had a cirrhosis of the liver with a moderate degree of jaundice. The prothrombin level was 63 per cent at the time vitamin K was given. An

initial 6 mg. dose brought the level to 100 per cent in one-half hour. The bleeding lessened but did not stop entirely. In our series of patients who were operated upon none was allowed to continue with low prothrombin levels without instituting vitamin K therapy. No abnormal bleeding occurred in these cases. Prothrombin determinations were made in various conditions in which bleeding was a characteristic manifestation (purpura, nephritis, leucemia, etc.). In none of these diseases was a delayed prothrombin time noted.

No correlation between the degree of jaundice or the duration of the jaundice and the plasma prothrombin level could be made. Five of our patients who had dangerously low levels did not have jaundice (Table II). Conversely, several severely jaundiced patients had normal prothrombin times (Table III). Thus, one may assume that

TABLE III

JAUNDICED PATIENTS WITHOUT DIMINISHED PROTHROMBIN ACTIVITY

CASE	DIAGNOSIS	JAUNDICE		PROTHROMBIN ACTIVITY
		DURATION	DEGREE*	
1. H. S.	Toxic hepatitis	2 mo.	4	100%
2. A. W.	Toxic hepatitis	2 wk.	1	100%
3. C. S.	Pancreatitis	1 wk.	1	98%
4. A. B.	Cirrhosis of liver	1 wk.	2	92%
5. C. M.	Cirrhosis of liver	1 wk.	1	100%
6. G. N.	Cirrhosis of liver	1 wk.	1	100%
7. H. B.	Carcinoma of pancreas	1 mo.	2	90%
8. H. M.	Postappendectomy pylephlebitis	3 days	1	89%

*Degree of jaundice: *1*, slight; *2*, moderate; *3*, severe; *4*, very severe.

jaundice in itself is not a criterion for the determination of prothrombin levels. From our observations it appears that any patient with biliary tract disease, with or without jaundice and with or without bleeding, should have a prothrombin determination if one wishes to eliminate entirely the danger of hemorrhage. Waddell and Guerry[19] and Kato and Poncher[20] recently studied the relationship of vitamin K deficiency to hemorrhage in the newborn; they noted favorable results following vitamin therapy.

CONCLUSIONS

Twenty-three patients with a delayed prothrombin time were treated by oral administration of synthetic vitamin K. Twenty-two of these patients responded favorably. One case, in a terminal condition as the result of a carcinoma of the rectum, gave only a 5 per cent increase in the percentage of clotting activity.

The dosage of the synthetic compound recommended is an initial dose of 6 mg. with 2 Gm. of bile salts (six capsules of 5 gr. each). The plasma prothrombin level is then maintained with 3 to 6 mg. of vitamin K and 2 Gm. of bile salts daily.

Bile salts are necessary with the vitamin K compound for the patients who do not have bile salts secreted into the intestinal tract.

A pronounced response to the synthetic vitamin K almost invariably occurs within one-half to one hour.

The amount of vitamin K necessary to maintain a normal percentage of clotting activity varies individually; thus, prothrombin determinations are guides to maintenance dosage.

No nausea or vomiting and no toxic effects were observed following large doses of the synthetic compound.

In biliary tract surgery the fourth to the seventh postoperative day constituted the period when the prothrombin activity most frequently reached dangerously low levels.

Hypoprothrombinemia may occur with or without jaundice and with or without bleeding; no definite relationship between the degree or the duration of the icterus and the decreased prothrombin levels can be made. However, it is true that prothrombin levels approaching the bleeding levels will be encountered more frequently in jaundiced patients, particularly if considerable liver damage is present.

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THE TREATMENT OF EXTERNAL FISTULAS OF THE PROXIMAL SMALL BOWEL

A Means of Temporary Mechanical Anastomosis

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THE treatment of external fistulas of the upper small bowel has always been a serious and difficult problem as is evidenced by the multiplicity of methods which have been devised. The seriousness largely depends on the character and extent of the lesion and to a greater degree on its site. The higher the fistula in the upper small bowel, the greater its danger up to that level in the second part of the duodenum described as "the duct-bearing portion"[1] and since spoken of as "the lethal line of Draper Maury." These fistulas, attended, as they usually are, by rapid loss of fluids, chlorides, and nourishment, produce a condition very similar to that caused by acute intestinal obstruction.[2] There rapidly ensues a rise in the blood nitrogen and a fall in the blood sodium and chloride ions.[3, 4] It has also been shown that the blood potassium rises in cases of complete intestinal fistula to toxic levels as found in acute intestinal obstruction, experimental adrenal insufficiency, and acute potassium poisoning.[5] This high potassium level is lowered by the administration of saline solutions. The loss of the digestive juices also is of importance as the loss of the pancreatic juice alone has been shown to be fatal.[6]

The occurrence of the fistula is distressing to the patient as it is realized immediately that something serious has occurred when with each ingestion of fluid by mouth there is an almost immediate gush of intestinal contents from the fistula. This mental distress is intensified by the physical one accompanying the ensuing digestion of the skin and tissue of the abdominal wall by the tryptic ferments.

Immediate operative surgical attack is not indicated in the great majority of cases due to the high mortality of about 50 per cent attending attempts at direct closure or side-tracking anastomosis. This mortality is directly related to the patient's poor general condition. Methods of conservative treatment are therefore indicated with the object of improving the patient's condition sufficiently to withstand the operative procedure. It may also be noted here that in certain cases these measures may in themselves result in healing.

The methods of treatment described may be classed as chemical, physical, mechanical, and surgical or combinations of these.

The chemical means are devoted to the minimizing or prevention of the digestive action of the juices on the patient's tissues by neutralization.

Received for publication, April 26, 1940.

In 1929 Potter[49] described the use of beef extract and N/10 hydrochloric acid, reporting the healing of several incomplete fistulas by this means alone. He advised the building up of a wall about the external opening of the fistula or about the margins of the draining wound with gauze, impregnated with beef extract and laying inside this wall gauze dripping with N/10 HCl. The pancreatic juice is used up by activating the beef extract and is neutralized by the HCl. The excess HCl is used up on the beef extract rather than on the skin and tissues.

In 1930 CoTui[7, 8] advised the use of kaolin, a colloidal absorbent for the electronegative trypsin. Its use has been reported frequently since, both alone and as an adjunct to other methods.

To lessen the skin excoriation the use of the continuous bath was advised by Cushing in 1899[9] and again recommended in 1919 by Ochsner,[10] who also found benefit from the feeding of egg white.[11] Cunningham[12] has advised the use of copper bronzing powder and in 1929 Rees[13] advocated dried milk as a dressing. Potter in 1932[14] suggested the use of the Bradford frame. With the opening of the fistula downwards and the intestinal wall pouting, the discharge from the fistula did not flood onto the patient's abdominal wall. In 1938 Dixon and Deuterman[15] noted the relief obtained by the patient from the tanning of the eroded skin surface by 10 per cent tannic acid.

It is easy to understand that methods of blocking the fistulous opening were among the earliest treatments advocated. The first recorded case is that of Reybard,[16] who used a wooden button in the lumen of the gut tied to a crossbar on the abdominal wall by a suture passing through the fistula. A button of leather was later recommended by Kleybolte in 1842.[17] Gauze soaked in oil has been used by Rigby,[18] Hendon,[19] Fechen,[20] and Stadler[21] to block the fistulous opening, and chewing gum recommended by Judd and Phillips[22] in those small fistulas which are not serious but leak and cause excoriation. Johnston[23] described the use of two small inflatable balloons placed about 1.5 cm. apart on a two-way catheter as a temporary closure. The inner balloon is inserted into the lumen of the bowel and inflated, then withdrawn into the fistulous tract until the second balloon appears on the surface. This outer balloon is then inflated to hold the first balloon in place. The inner balloon tightly wedged in the fistulous tract effectively closes the opening. In 1917 Dowd[24] described a double metallic button which has been used successfully also by Mayo[25] and Cattell.[26] Kappis[27] in 1911 used a T-tube with the straight part of the tube providing a channel between the upper and lower parts of the bowel with the right-angled part protruding through the fistula, blocking it and providing drainage for overflow. This method has been used by Kaehler[28] and Pamperl[29] and also by Ahrens,[30] who points out that the straight part of the tube tends to depress the spur on the mesenteric side of the bowel.

As late as 1938 Marshall and Lahey[31] pointed out the lifesaving value of ordinary buttons, one on the inside of the bowel tied to another on the abdominal wall, as an emergency treatment. Hartzell[32] in the same year described in detail how he makes a disk of soft rubber to fit accurately the inside of the bowel at and about the fistulous opening. The rubber disk is held in place by a thread fixed externally. He finds this method particularly valuable where there is a fairly large opening in a presenting knuckle of bowel.

The use of suction in some form has been found by Cheever,[33] Lahey,[34] Walters, Kilgore, Bollman,[3, 4] and Ochsner[10] to be a very practical means of dealing with the fluids from the afferent loop. It has been used for the simple removal of the offending discharge and also for the collection of the fluids extruded for readministration to the patient.

Cameron in 1923[35] reported the use of an electric suction apparatus connected to a catheter with several additional holes inserted into a duodenal fistula following gastric resection with cure.

Bohrer and Milici (1931)[36] in the treatment of duodenal fistula advised dilating the opening and introducing into it a half-inch fenestrated rubber tube to act as a reservoir. Into this large tube was placed a small rubber catheter attached to a vacuum bottle. The discharge was thus removed as quickly as it accumulated. They advised also that the vacuum be maintained by a water pump as all electric suctions will become heated by continuous use. They discontinued all food by mouth except water, which dilutes the discharge and allows the suction to work better. Their patients were fed by nutrient enemas, glucose by vein, or hypodermoclysis.

In 1937 Tenopyr and Shafiroff[37] reported a method combining chemical and mechanical means whereby the intestinal contents were removed from the bowel without skin irritation. A Murphy drip tube is fitted into the center of a large soft rubber doughnut pessary which is bound tightly over the fistula by a bandage about the body, the tip of the Murphy drip tube just entering the opening of the fistula. Kaolin is packed between the pessary and the skin. A Wangensteen suction apparatus attached to the tube removes the fluid into a container by the bed.

Another method combining the use of kaolin and suction was described by Dixon and Deuterman in 1938.[15] They place a suction tube through a wall that is built about the external stoma. The wall is constructed of adhesive tape and a paste made of kaolin and water on the freshly cleansed skin. The tip of the soft rubber fenestrated suction tube is placed partially inside the external stoma of the fistula.

The feeding of these patients and the return of the fluids collected have been accomplished by various means.

The introduction of liquid food by jejunostomy has been recommended by Bohrer and Milici,[36] McGuire,[38] Lewisohn,[39] Erdman,[40] Kelling,[41]

Pannet,[42] Dixon and Deuterman.[15] Einhorn[43] passed a duodenal tube beyond the fistulous opening for feeding. In 1927 Marogna[44] reported passing a long tube through the fistula into the jejunum through which food was introduced. Erdman in 1921[40] reported in the treatment of duodenal fistula the use of continuous suction into a bottle by the bed, and the return of these materials through a jejunostomy tube through which the patient also was entirely fed. This patient recovered but developed a parotitis which resolved without external suppuration. He also introduced saline solution by a Murphy drip into the jejunostomy tube. Dixon and Deuterman (1938)[15] also advocated this method.

Fox in 1936[45] suggested collection of fluids by suction and their return by proctoclysis.

Wilkie[46] introduced two catheters, one in the afferent connection with another in the efferent loop. Volkman[47] and Peet[48] found this method valuable.

Where the lesion is small or is a simple fistulous tract leading to bowel which is in continuity, the problem is a less serious one and in these cases simple suction, the use of neutralizing substances, or means of temporarily blocking the fistulous opening may result in healing. Sometimes the disagreeable leak with accompanying digestion of surrounding skin is the most troublesome problem as the patient's nutrition and metabolism may not be seriously impaired.

Where, however, there is complete severance of continuity of the upper small bowel or a very large opening, the problem becomes one of more emergent character and lack of adequate treatment is rapidly fatal. In these cases all the contents of the small bowel are discharged on the skin surface; the loss of nourishment and fluids is total and hypochloremia with toxemia rapidly ensues. Digestion of the abdominal wall is rapid and extensive.

Such a case occurred in the wards of the Montreal General Hospital in 1929. A summary of the history is as follows:

CASE REPORT.—Mrs. H. P., aged 46 years (Hospital No. 7295/28), was admitted to the Montreal General Hospital, Dec. 19, 1928, with a perforated diverticulum of the sigmoid colon. The perforated mass of bowel was extraperitonealized as a colostomy through the exploratory wound and though very ill for a time due to the fecal generalized peritonitis, she recovered. Closure of the colostomy was later done and on the third day after this operation leakage through the wound was noted, and by the seventh day examination of the wound showed six open ends of small bowel presenting in pairs at intervals in the wound. The intestines, herniating through the disrupting wound, had pressed upon the silkworm gut sutures used to close the skin and had been completely cut through in three places. The skin about the wound was excoriated and the patient's condition deteriorating. Saline and glucose solutions were given intravenously. The openings of the upper and lower portions of bowel were determined, and, using the open end of a tube over the proximal opening, continuous suction was applied. The collected fluids, with other fluid nourishment, were fed back into the distal loop by a catheter at intervals of two hours by day and three hours by night. Fluids by mouth were discontinued. All varieties of substances

then available were employed on the abdominal wall in efforts to prevent its digestion, but with each peristaltic wave of the upper jejunal loop intestinal contents with digestive juices gushed over the abdominal wall as the ordinary suction apparatus was unable to cope with it. Especially was this so when occasionally anything was given by mouth. Despite all efforts and treatments, the patient gradually and progressively deteriorated, became extremely emaciated, and required stimulants at frequent intervals to keep her alive. It was quite obvious that unless something more could be done she would very soon die. The digestion of the skin of the abdominal wall was very extensive. All available superficial veins eventually became thrombosed and fluids had finally to be given by subcutaneous injection or by cutting down on deeper veins.

After trying out several methods of re-establishing the continuity of the small intestine by external means, at this point, thirty-eight days postoperative, an apparatus was devised which was successful. This device removed mechanically all the contents of the upper loop and automatically transferred them to the lower loop without any spilling, feeding them slowly into it so that they were readily absorbed. There was no further loss of electrolytes and digestive juices from the intestinal tract, and with the additional morale given the patient by being able to take fluids and nourishment by mouth, there was rapid improvement. All varieties of clear fluids could be given and the patient was encouraged to drink them freely as the apparatus had no difficulty in handling large amounts. Practically the only precaution necessary was to forbid giving foods which would block the holes in the tubing. Milk could not be given as it is coagulated in the stomach. Nourishment, in addition to that taken by mouth, was given through the apparatus in the form of glucose solution. As the transfer of fluids from one loop to the other was continuous and automatic, a minimum of attention was required. Minor adjustments to the tubing in the bowel were all that was necessary, and this about once a day.

Subcutaneous fluids were discontinued in twenty-four hours and stimulants were decreased on the fourth day. The intestinal contents did not come in contact with the abdominal wall; there was no soiling and the digested areas rapidly healed so that by the tenth day the abdominal wall was "dry and almost healed."

On the nineteenth day after the apparatus was put into use the patient was sufficiently recovered to withstand operation. Preceded by blood transfusions, a successful shortcircuiting anastomosis was performed through a completely healed abdominal wall.

At a subsequent operation months later, the shortcircuited loops of bowel opening onto the abdominal wall were excised.

The apparatus is activated by continuous suction and its construction is simple. A fenestrated rubber tube 5 to 6 inches in length (the tip of a large rectal tube with additional holes cut in its sides works admirably) is inserted into the proximal or afferent loop and held in by tapes tied about its outer end secured to adhesive strips on the sides of the abdomen, or to a band about the back. Into this "well" is inserted a soft rubber catheter which has had several additional small openings made in its terminal 2 to 3 inches. This catheter is attached by rubber tubing to the top of a reservoir which is a glass tube 1¼ inches in diameter and 2 feet long with a rubber stopper at either end. This glass tube is held in a vertical position by a laboratory clamp and stand set on a bedside table. Inserted also into the upper end of this closed reservoir

is a tube leading to the suction. From the bottom of the apparatus a single tube leads directly to another soft rubber catheter which is inserted for almost its full length into the distal or efferent loop of bowel.

When suction is applied, small amounts of fluid and air rise alternately in the afferent tube, spilling over into the reservoir; the continuous column of fluid in the reservoir and the efferent tube causes the fluids to flow slowly and continuously into the efferent loop of bowel. Glucose solution may be added to the intake by inserting a T-tube in the afferent rubber tube just before it empties into the reservoir. A douche can is

Fig. 1.—Photograph of original apparatus in use.

connected to it through a Murphy drip and the rate of flow controlled by a stopcock. Only a moderate amount of continuous suction is required to activate the apparatus. The suction system with which our surgical wards are equipped was used in this case, but suction from a water pump would work very well.

The importance of restoring the fluid and electrolyte balance cannot be overestimated. This phase of treatment has been emphasized and detailed recently by Coller and Maddock[50] so will not be further discussed here. There would appear, however, to be some factors contained in the normal digestive juices which cannot as yet be replaced

by intravenous therapy but are returned to the patient by the restoration of the fluids lost through the fistula and contribute markedly to recovery.

It would seem that the only indication for surgery in the early treatment of these cases would be in those where an obstruction is present below the fistula or where, for some other reason, a soft rubber catheter cannot be passed. If it is impossible to pass a catheter into the lower loop, a jejunostomy should be performed to receive the efferent catheter. Where the opening is in the side of presenting bowel, the fenestrated tube or "well" may be inserted in the afferent side of the spur and the efferent catheter into the distal one. Where the fistulous tract is long and the opening high in the intestinal tract, the "well" may be inserted into the fistula and the efferent tube led to a duodenal tube whose tip has been passed well beyond the fistulous opening as suggested by Einhorn.

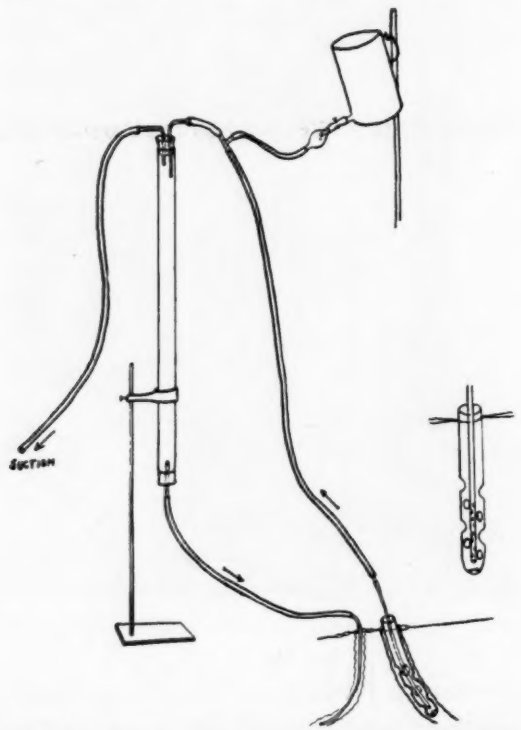

Fig. 2.—Diagram of apparatus showing: fenestrated tube forming "well" in proximal loop or in fistula, with fenestrated catheter in place; the connected irrigating can from which glucose solution, for additional nourishment, enters the apparatus; glass tube reservoir; catheter inserted into the efferent loop or into a jejunostomy; tube leading to suction. The direction of circulation is indicated by arrows.

SUMMARY

1. The pathological physiology of proximal external small bowel fistulas is briefly summarized.

2. The various methods used in their treatment are reviewed.

3. A simply made apparatus for temporary mechanical anastomosis, activated by continuous suction, is described.

4. A case of multiple complete jejunal fistulas, in which the above apparatus was successfully used, is reported.

Since this article was submitted for publication, two more cases have been successfully treated by this method on the surgical service of Dr. F. B. Hurd at the Montreal General Hospital.

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PATHOLOGIC STUDY OF HYPERTROPHIC ARTHRITIS OF THE HIP*

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THE disease of the hip characterized clinically by moderate or severe pain on motion, with creaking and grating, with no marked deformity except in very advanced cases, and with stiffness of the joint after periods of rest and variously known as hypertrophic arthritis, degenerative arthritis, arthritis deformans, osteoarthritis, morbus coxae senilis, and by many other terms is one of the common causes of discomfort and disability in the middle and later years of life.

The advances made in the study of its causation and prevention have been negligible in comparison with those made in the same fields in other diseases, or even in other forms of arthritis, and this is particularly true in proportion to the amount of disability caused by it. In a review of the literature on arthritis for 1937, Hench found only six articles of more than 700 in which hypertrophic arthritis was the sole or chief topic, and he came to the conclusion that it "remains a neglected stepchild in the family of rheumatism."

It might be assumed from the foregoing discussion that the treatment of hypertrophic arthritis is in as sad a state as is our knowledge of its causation, since the efficacy of therapeutic procedures for any disease depends largely on a thorough knowledge of its causative factors. Such is the case, although within comparatively recent years numerous procedures of one sort or another have been devised to alleviate the symptoms. The various forms of physical therapy are still the most common forms of treatment and in most cases will give a considerable degree of temporary relief. Diets, vaccines, and other similar methods, on the whole, are useless. Surgical procedures, consisting of manipulation under anesthesia, cheilotomy and remodeling of the head of the femur, acetabuloplasty, and forage of the head and neck of the femur, are sometimes indicated in painful hypertrophic arthritis. Arthrodesis, according to Henderson, is usually refused by the patient although it is certainly the procedure of choice in those patients whose occupations include heavy labor. Roentgen therapy is sometimes used, with occasional favorable results.

ETIOLOGY OF HYPERTROPHIC ARTHRITIS

Inasmuch as the cause is not definitely known, it was thought that a brief review of the most widely accepted hypotheses might aid in under-

*Abridgment of thesis submitted by Dr. Sawyer to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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Received for publication, May 8, 1940.

standing or interpreting the various pathologic changes which are found. It must be remembered in a discussion of the etiology, if not of the pathology, that hypertrophic arthritis may be either primary or secondary and that the latter may be the sequela of traumatic arthritis or of the various forms of infectious or metabolic arthritis. Some authors, notably O'Reilly, have maintained that the secondary types should not be included in a discussion of hypertrophic arthritis, since they are not the true primary type of osteoarthritis. However, the pathologic changes are the same, and they will be considered together in this paper.

Trauma of a localized form must be given a place of prominence in any discussion of the etiology. Opinions vary from that of Fisher,[3, 4] who said that in this group it forms almost the sole etiologic factor, to that of Jones, who expressed the opinion that it may be a determining but not an actual cause. Fisher expressed the opinion that the most important type of trauma in the production of hypertrophic arthritis is the frequently repeated microtrauma, rather than a single, severe contusion of a joint. He also pointed out the fact that there may be posttraumatic inflammation of a joint without the presence of infection. When posttraumatic intra-articular changes do occur, they are hypertrophic in character and pathologically the same as primary (senescent) hypertrophic arthritis. When the etiologic factor is a single acute contusion, it may be years before the hypertrophic changes appear, at which time it may be impossible to draw an analogy between a possibly youthful victim of trauma and a senile patient with hypertrophic arthritis. If such an acute injury resulted in a residual deformity, however, and particularly if at the time the patient presented himself the arthritis were monarticular or more severe in the traumatized joint than in untraumatized joints, such an analogy would be logical. In a recent review of 150 cases of hypertrophic arthritis of the hips, 20 per cent gave a definite history of previous severe trauma of the involved joint.

The association between hypertrophic arthritis and arteriosclerosis was noted by many of the older physicians, and for a time this was one of the favorite explanations for the occurrence of the disease, but any direct evidence that osteoarthritis may occur secondarily to arteriosclerosis is very scanty and most modern observers discount this hypothesis. Numerous experiments have been done in an effort to support this hypothesis, however, notably those of Wollenberg, who tied the patellar vessels of a dog and noted that this was followed by overgrowth of the patella, with evidence of degeneration of the articular cartilage and hypertrophic changes. Fisher subscribed to this hypothesis to the extent that he admitted the possibility that arteriosclerotic changes may contribute to the decreased nutrition of degenerating cartilage, but, in view of the absence of sclerosis in early cases of osteoarthritis, he expressed the opinion that the coexistent arteriosclerosis and osteoarthritis have a common cause. Hench found in the literature on osteoarthritis

that the incidence of arteriosclerosis was no greater in osteoarthritis than in a similar age group without osteoarthritis and came to the conclusion that little or no support could be found for the hypothesis.

The inclusion of hypertrophic arthritis in the great group of diseases formerly classified under the single heading "rheumatism" and its consequent association in the minds of physicians and laymen with the infectious types of arthritis naturally have led to the formulation of numerous hypotheses of its causation based on the premise that it, too, was the result of infection. At the present writing, no organism has been found in osteoarthritis, and in view of the clinical course of the disease it seems unlikely that any specific organisms ever will be found within the joint. On the other hand, it is well recognized that in the more destructive types of infectious arthritis new bony formations and changes are encountered which are characteristic of hypertrophic arthritis. Kaufmann stated that it might follow infectious arthritis or chronic purulent synovitis, and Albee and Preston[1] said that it may become engrafted on healed arthritis of a tuberculous or pyogenic type. In general, the various authorities consulted agreed that osteoarthritis might supervene in a joint previously injured by bacterial invasion but, other than that, bacterial infection seemed to have no part in the picture.

There may be some obscure bond between osteoarthritis and the ductless glands, but it has never been definitely proved that the incidence of endocine dysfunction is greater in those suffering from osteoarthritis than it is in others in the same age group who do not present symptoms of arthritis. Fisher expressed the opinion that disordered endocrine function plays an important part in osteoarthritis, particularly the type seen in women at the menopause. He stated further that the same type of arthritis may be found in younger women after an artificial menopause, and Llewellyn said that the resistance of a patient to osteoarthritis is lowered after thyroidectomy or the exposure of the thyroid to roentgen rays. According to both McCarrison and Llewellyn, osteoarthritis is more common in regions of endemic goiter than one would normally expect. Favorable results are sometimes obtained by giving thyroid to osteoarthritic patients, but the probabilities are that the improvement noticed is due to a general improvement in body economy rather than to any specific effect of the thyroid hormone on the arthritis.

PATHOLOGIC CHANGES AS DESCRIBED IN THE LITERATURE

Changes in the Articular Cartilage.—Ziegler expressed the opinion that the cartilage may still be intact at a time when there is already considerable deformity of the head of the femur. On the other hand, Fisher said that the first change observed by him is an alteration in the normal color and translucent appearance of the cartilage, particularly the central portion where he assumed that the circulation is inadequate. Jones bore him out in his assertion that the first changes are at the

center of the cartilage. The cartilage soon begins to show some microscopic changes with an alteration in the staining reaction of the matrix, but with as yet no changes in the cartilage cells. At a slightly later stage, according to Fisher, fibrillation of the matrix and degeneration of the cells near the articular surface of the cartilage appear. He pointed out the obvious fact that there is no invasion of the cartilage by fibrous tissue at this stage and stated that by "fibrillation" he meant a mere splitting of the matrix. As the degeneration of the cartilage progresses, the cellular elements degenerate and one may observe deposits of calcium salts in the deeper layers of the matrix. Finally, the cartilage may be completely worn away from the subchondral plate.

According to MacCallum the changes are predominantly in the cartilage, which first becomes fibrillated or plushlike, and Stockman observed that the cartilage was early dulled in color, suffering a loss of its normal "polish," subsequent to which small elevations appeared over its surface with larger irregular masses at the margins of the joint, consisting of spongy bone covered with cartilage. The matrix at this stage may be normal or fibrillated, and there is active proliferation of the cartilage cells. Later the matrix becomes definitely fibrillated, the more superficial layers horizontally, the deeper layers vertically, and the top layer is worn away, leaving the lower furlike layer with actively proliferating cartilage cells which are discharged into the joint space.

According to Fisher, the small elevations appearing over the surface of the cartilage, and observed by Stockman, are properly called epiarticular ecchondroses, in distinction from periarticular ecchondroses, and are the result of invasion of the deeper layers of the cartilage by osteoid tissue with the formation of new bone, or the result of ossification in the cartilage itself which has previously undergone hyperplasia of some sort. It is pointed out that these ecchondroses may become detached to form loose bodies in the joint.

Fisher expressed the opinion that the more competent circulation at the periphery of the joint explains in large part the formation of the periarticular ecchondroses (Fig. 1). He observed that, when the degeneration of the central cartilage was well advanced, the marginal cartilage showed signs of hypertrophy, producing the condition known as "lipping." These periarticular ecchondroses are eventually invaded by osteoid tissue, as were the epiarticular ecchondroses, and become ossified to form a chondro-osteophyte. They may later become eburnated under the proper conditions and have been known to break off to form loose bodies in the joint cavity. According to Nichols and Richardson,[13, 14] these marginal exostoses usually appear first in the capsular attachments, and they agree with Fisher that they form an actual increase in the size of the articular surface.

Pathologic Changes in the Bone.—The most striking change in the bony structures is the thickening of the subchondral plate and its sub-

jacent trabeculae, particularly in the regions of eburnation. According to MacCallum, when the bony surface is exposed, the resultant irritation due to the motion of the joint sets up the formation of new bone, the surface layers becoming hard and compact. If a large enough area of bone is exposed, it may be worn away deep into the epiphysis, resulting finally in a mushroom-shaped head.

Fisher observed that the exposed surface of bone became "polished and glistened like porcelain," and that frequently its surface was marked with grooves which he thought were produced by the epiecchondroses or periecchondroses of the opposed articular surface. He also said that the subchondral plate may show evidence of thickening and increased density before the cartilage has disappeared, and Ziegler

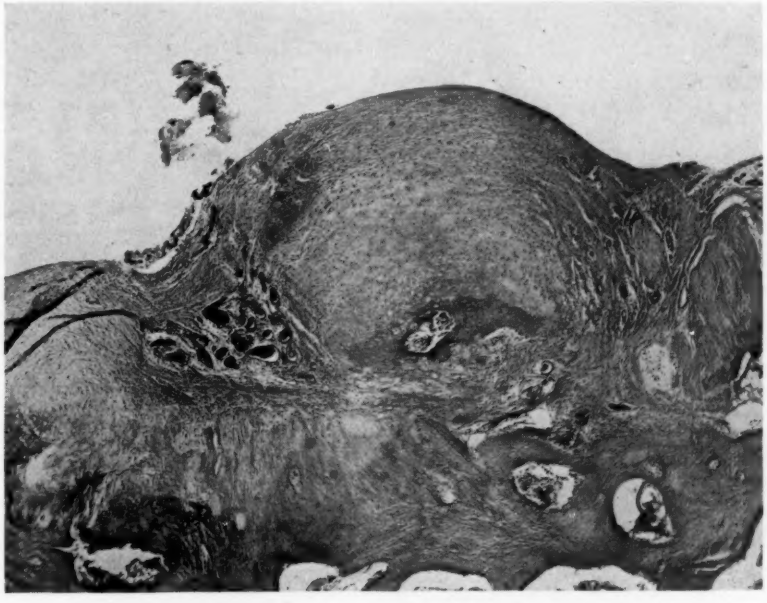

Fig. 1.—Periarticular ecchondrosis, with formation of new bone, just below its center, and increased thickness of the subchondral plate (Case 17, ×25).

thought he observed these changes even before the cartilage showed evidence of degeneration. Stockman and Shattock studied the surface of the eburnated bone and observed that the Haversian canals opened on its surface as the bone was gradually worn away, thus proving, if there were any doubt, that the eburnated surface is composed of true bone. Stockman also expressed the opinion that the Haversian canals were invaded by many small blood vessels, possibly resulting in atrophy and absorption of the underlying bone.

Allison and Ghormley, besides observing some of the foregoing pathologic changes, also noted an increased thickness of the trabeculae subjacent to the regions of eburnation.

Pathologic Changes in the Bone Marrow.—The characteristic changes observed in the marrow consisted, briefly, of fibrosis or its variations.

So-called cysts filled with loose fibrous tissue were seen by most of the observers, and in many instances the marrow had apparently been replaced by fat tissue. The fibrosis of the marrow spaces was apparently particularly evident in the region of the subchondral plate.

Pathologic Changes in the Synovial Membrane and Capsule.—At the same time that lipping of the articular margin appears (Fisher), the synovial membrane proliferates with the formation of new villi and hypertrophy of the old villi. Later in the disease the membrane may become atrophic and comparatively smooth. When examined microscopically, the villi are seen to be very vascular and most of the synovial tissue has been replaced by fibrous tissue. Cartilaginous bodies may form in the villi, later to be broken off to form loose bodies in the joint cavity.

Changes in the joint capsule were apparently not observed, although Fisher mentioned that the capsule may "migrate" to accommodate itself to the changing shape of the head of the femur.

PATHOLOGIC OBSERVATIONS ON OUR MATERIAL

The percentage frequency of different pathologic features in the nineteen cases on which this paper is based is shown in Table I.

TABLE I

PERCENTAGE FREQUENCY OF DIFFERENT PATHOLOGIC FEATURES IN 19 CASES OF HYPERTROPHIC ARTHRITIS OF THE HIP

PATHOLOGIC FEATURES	NO. OF CASES	PER CENT OF TOTAL	CORRECTED PERCENTAGE*
Degeneration of articular cartilage	15	79	100
Fibrillated cartilage	13	68	87
Pitted cartilage	12	63	80
Proliferation of marginal cartilage	9	47	100
Increased calcification of deeper cartilage matrix	15	79	100
Increased thickness of subchondral plate	15	79	100
Eburnation	11	58	73
Increased thickness of trabeculae subjacent to eburnation	11	58	100
Atrophic marrow	16	84	100
Osteoid tissue formation	16	84	100
Fibrosis cystica	10	53	66
Fibrous synovial membrane	15	79	100
Arteriosclerosis	11	58	58
Collections of lymphocytes in synovia or marrow	0	0	0

*In computing the corrected percentage, those cases were eliminated in which a particular type of tissue change did not appear in the specimen; for instance, eburnation appeared in only 58 per cent of the 19 specimens studied, but it appeared in 73 per cent of the 15 specimens in which at least part of the articular surface was present.

The gross examination of the specimens studied revealed evidence of degeneration of the articular cartilage in every case in which cartilage was a part of the specimen. For the most part, the cartilage was dull and had lost its normal translucent appearance, and on a few specimens

small areas of grayish tan discoloration were seen. Proliferation of the marginal cartilage was present in every case in which part of the margin of the articular surface was present, and in these regions the cartilage seemed to be in a better state of preservation. It was not as soft as was the cartilage in the central areas of the articular surfaces, was pearl gray in color, and in a few instances gave a definite translucent appearance. Numerous small pits were observed in some of the sections, principally in the region of the central articular area.

Fig. 2.—Vertical fibrillation of the cartilage matrix (Case 1, ×90).

Numerous areas of eburnation were found, varying in size from a few millimeters to several centimeters, and they invariably presented a highly polished, glistening appearance. On cross section of the specimens it was seen that the subchondral plate was thickened in most cases in the eburnated areas, and the cancellous portion of the bone also seemed to be more abundant subjacent to these areas. These changes were not observed in those regions still protected by the articular cartilage.

No definite conclusions could be reached as to the condition of the marrow. Synovial tissue, when present in large enough amounts to examine grossly, seemed to be firm and fibrous in character.

The microscopic examination revealed degeneration of the articular cartilage in every instance. Some beautiful examples of both longi-

tudinal and vertical fibrillation of the matrix were seen, accompanied in most instances by irregular staining qualities (Fig. 2). The longitudinal fibrillations were much finer in character than the vertical fibrillations, with an occasional pyknotic chondrocyte lying among the "fibers" here and there. Pitting of the cartilage was observed in some of the specimens, and some of them appeared to be filled with a loose

Fig. 3.—Increased deposition of calcium salts in the deeper cartilage matrix (Case 3, ×90).

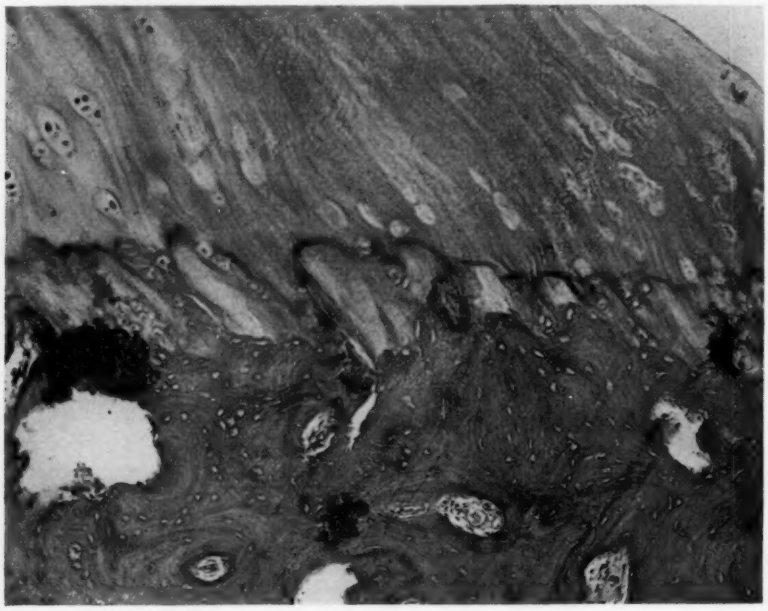

Fig. 4.—Fibrillation of the cartilage and increased calcification of the deeper matrix, with increased thickness of the subchondral plate (Case 14, ×95).

fibrous tissue or pannus in which there was no evidence of lymphocytic infiltration. Most of the cartilage cells were pyknotic, and this was particularly true of those cells near either surface of the cartilage. No definite evidence of proliferation of the cells was found in any of the degenerating cartilage. In numerous instances the cartilage adjacent to the subchondral plate had been invaded by fibrous tissue from the marrow which, in some cases, had dedifferentiated into osteoid tissue with evidence of the formation of new bone. Increased deposition of calcium salts in the deeper matrix was found in all the specimens (Fig. 3).

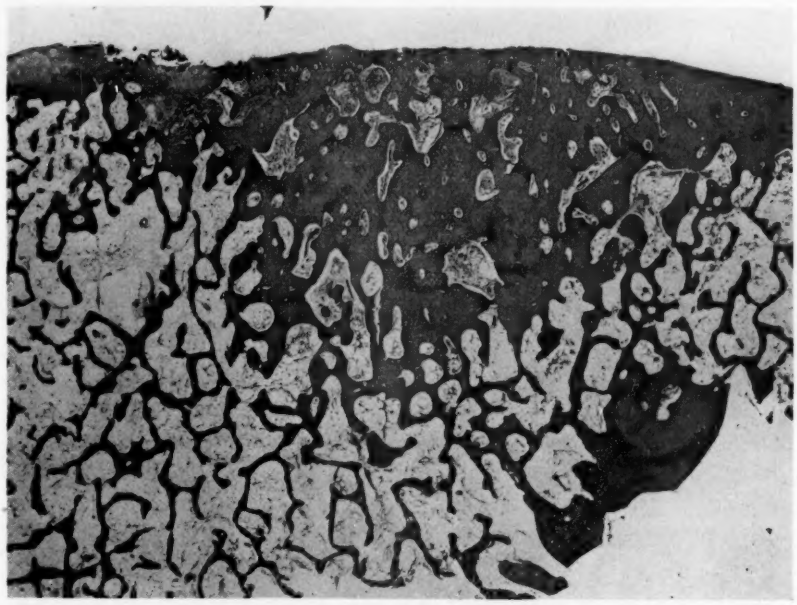

Fig. 5.—Eburnation with increased thickness of the subchondral plate and its subjacent trabeculae, which have united to form almost a solid pyramid of bone extending into the head of the femur. Marked activity of osteoid tissue in the marrow spaces included in this region (Case 17, ×6).

The most striking change noted in the bone was the increased thickness of the subchondral plate (Fig. 4), chiefly in the regions of eburnation. Slight increases in its thickness were noted subjacent to areas where the cartilage was markedly degenerated, but under areas that were still protected by a moderately thick layer of cartilage the subchondral plate was not thickened and, in some instances, was even thinner than normal. In the regions of eburnation there was usually extensive formation of new bone in the marrow spaces immediately subjacent to the subchondral plate with increased thickness of the trabeculae as well as of the plate. It was evident that the marrow had been replaced by fibrous tissue which had dedifferentiated into osteoid tissue with subsequent calcification. This chain of events was almost never seen in those areas which were still protected by a layer of cartilage, no matter how degenerate, but it was observed that in numer-

Fig. 6.—Intramembranous ossification in a marrow space subjacent to an area of eburnation (Case 3, ×80).

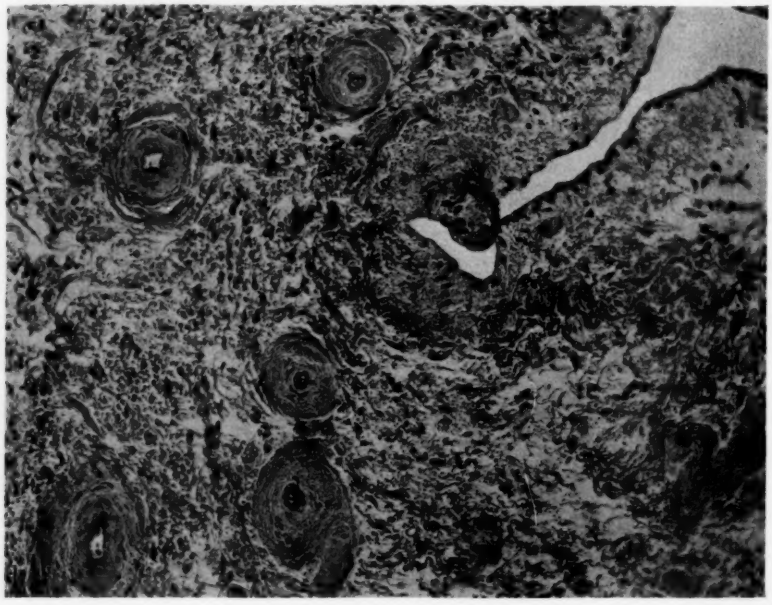

Fig. 7.—Marked arteriosclerosis and fibrosis of the synovial membrane (Case 4, ×110).

ous spots the subchondral plate and lower cartilage matrix had been invaded by small wicks, so to speak, of fibrous tissue which, in some instances, had dedifferentiated into osteoid tissue with the formation of small islands of bone in the cartilage matrix adjacent to the subchondral plate. This latter process seemed to be an endochondral ossification rather than the intramembranous ossification observed under the areas of eburnation. The manner in which the trabeculae under the eburnated areas had thickened and "gathered together," so to speak, to form a support for the subchondral plate was remarkable, and in two instances almost a solid pyramid of bone was observed extending into the cancellous portion of the head (Fig. 5). Many of the bone cells, particularly in the areas of eburnated bone, were pyknotic, and Haversian canals were observed opening onto the surface of the eburnated areas.

Fig. 8.—Atrophy of marrow, eburnation, and thickening of trabeculae and subchondral plate (Case 7, ×4).

The great majority of the marrow spaces had become filled with fat tissue although, as described previously, the spaces adjacent to the subchondral plate were frequently filled with either osteoid tissue or fibrous tissue (Fig. 6), giving the appearance of osteitis fibrosis cystica. In a

few fields fairly normal marrow tissue was seen, but even here there had been much replacement by fat cells.

The synovial tissue invariably showed evidence of fibrosis, with markedly increased vascularity (Fig. 7). The sclerosis of the vessels was graded according to the method of Kernohan, Anderson, and Keith[9, 15] and varied from no evident sclerosis in 5 of the 19 cases studied, to Grade 3 sclerosis on a basis of 1 to 4 in 2 of the cases. Of the remaining 12 cases, one was graded 0 to 1, two were graded 1, two were graded 1 to 2, five were graded 2, and in two the grade was not stated.

Fig. 8 shows the association of several of the foregoing changes in the same case.

SUMMARY AND CONCLUSIONS

Nineteen specimens of hypertrophic arthritis of the hip have been studied, and the pathologic changes observed have been described. It was found that:

1. The initial degenerative changes appear in the cartilage and are characterized by fibrillation, pitting, degeneration of the cartilage cells, and increased calcification of the deeper matrix.

2. The marginal cartilage proliferates and shows few of the signs characteristic of degeneration.

3. As the cartilage disintegrates and is worn away, the bone is exposed and becomes eburnated with thickening of the subchondral plate and the subjacent trabeculae by means of intramembranous ossification.

4. The subchondral plate may or may not be thickened. The trabeculae are almost never increased in size in those areas that are still protected by cartilage, and most formation of new bone in these areas is of the endochondral type.

5. The normal marrow is replaced by fat or loose fibrous tissue which, in some instances, dedifferentiates into osteoid tissue.

6. The synovial membrane is invaded by fibrous tissue with markedly increased vascularity.

7. Little evidence was found to support the hypothesis that arteriosclerosis is an etiologic factor of osteoarthritis.

8. Finally, no collections of lymphocytes were found which are characteristic of the infectious types of arthritis.

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THE TREATMENT OF TUMORS OF THE SHOULDER REGION BY INTERSCAPULOTHORACIC AMPUTATION

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EXCEPTIONALLY the occasion arises where it seems justifiable to remove the arm with the shoulder girdle in the treatment of tumors when less drastic measures have proved to be ineffective. The loss of this part of one's anatomy is not only extremely crippling and disfiguring, but the extensiveness of the operation is of sufficient magnitude to carry with it an appreciable mortality. Therefore, it is a point requiring considerable surgical acumen to determine correctly the time when less radical measures should be abandoned in favor of interscapulothoracic amputation.

Occasionally this operation may be indicated following trauma to the shoulder, rarely for an inflammatory process such as that described by Milch,[1] but undoubtedly the most frequent indication will continue to be a relatively benign radioresistant tumor that cannot be widely enough excised locally, due to nearness to structures important to the arm, to prevent local recurrences; in other words, tumors that are locally malignant due to their anatomical location and not from their morphologic composition.

Most probably the more malignant lesions will continue to be treated by local excision and/or irradiation until the biologic properties of the lesion have asserted themselves and metastatic deposits preclude more than efforts at symptomatic relief. Few surgeons would have the temerity to insist on radical amputation when first confronted with such a lesion in its virgin state, and a person who would submit to such a deforming and crippling operation without first giving conservative measures a trial scarcely can be imagined. The two following case records, we believe, exemplify the types of lesions in which interscapulothoracic amputation will most frequently be of value.

CASE REPORTS

Case 1.—A part Hawaiian male first came under our care on Jan. 13, 1923, at the age of 31 years, complaining of a swelling in the posterior region of the left shoulder. He attributed his trouble to having been struck by a baseball in this region in 1914. However, it was not until 1918 that a swelling was first noticed in this area. This tumor was removed at that time. It recurred and was removed along with the scapula in 1919. In July, 1922, a twenty-two-pound mass was again removed from the back of the shoulder. On Feb. 7, 1923, the mass in the posterior part of the shoulder, as shown Fig. 1, and a smaller one above the clavicle were removed, and 200 mg. of radium were implanted into the wound and left for twenty-three hours.

Received for publication, May 4, 1940.

Recurrence took place, and tumors of varying sizes about the shoulder were removed on Dec. 22, 1923, July 15, 1925, and Nov. 14, 1925. Radium was implanted into the wound on each occasion, the largest exposure being given on Nov. 14 when 200 mg. of radium were allowed to remain for forty-eight hours. All during this time the patient stoutly refused to submit to an operation that would sacrifice the arm. From the large doses of radium used, severe radium burns resulted. However, on March 29, 1926, the patient returned with a beginning gangrene of the fingers. The arm was cold and cyanotic, and the radial pulse was barely perceptible. A large recurrence had taken place in the axilla which had involved the axillary vessels. On March 31, 1926, the arm, including the clavicle, was removed, but a wide dissection of the axilla did not seem justifiable at this time because of the patient's rather poor condition. One month later, on April 26, 1926, the patient meanwhile having greatly improved, a very radical removal of the involved area was carried out. The subclavian vessels were ligated medial to the anterior scalenus muscle. The cervical nerves giving rise to the brachial plexus were severed in the same region. A

Fig. 1.—Showing scars of previous operations and a large recurrence on the posterior aspect of the shoulder.

wide circle of skin was made and carried down to include a large portion of the pectoralis major and minor muscles and the anterior edge of the trapezius muscle. A portion of the second rib that had become necrotic was removed, along with the axillary contents, well below the recurrence and down to the chest wall. The dissection was carried so high on the subclavian vein that injury to the thoracic duct took place, as evidenced by a spill of considerable chyle into the operative wound. A gauze pack was placed in the area from which chyle was seen to ooze, and, when it was removed several days later, no further discharge of this nature was seen. Following the operation an uneventful recovery took place, and no evidence of recurrence has since been noted. This individual has carried on with his work as a court stenographer and in spite of the loss of the arm and shoulder is able to hunt and shoot birds with considerable accuracy. Many details in the conduct of this case have been omitted for the sake of brevity, such as x-rays for possible metastasis, transfusions, and minor complications.

Pathologic Findings.—With tissue from the first conservative operation the first cut of the knife revealed the fact that the tumor was obviously a chondroma, but the preparation of sections and their interpretation presented certain obstacles. The tissue was so soft and slippery and in places so mucinous and myxoid that it was most difficult to prepare frozen sections. When blocks of tissue were dehydrated for paraffin embedding, they shrank to about one-quarter of their size. No one block of tissue looked like another, and the arrangement and architecture were most uneven. The tumor was traversed by septae that carried blood vessels; in the neighborhood of these vessels the cartilage cells were numerous, small but unequal in size, clumped together in groups, apparently growing rapidly, and crowding each other,

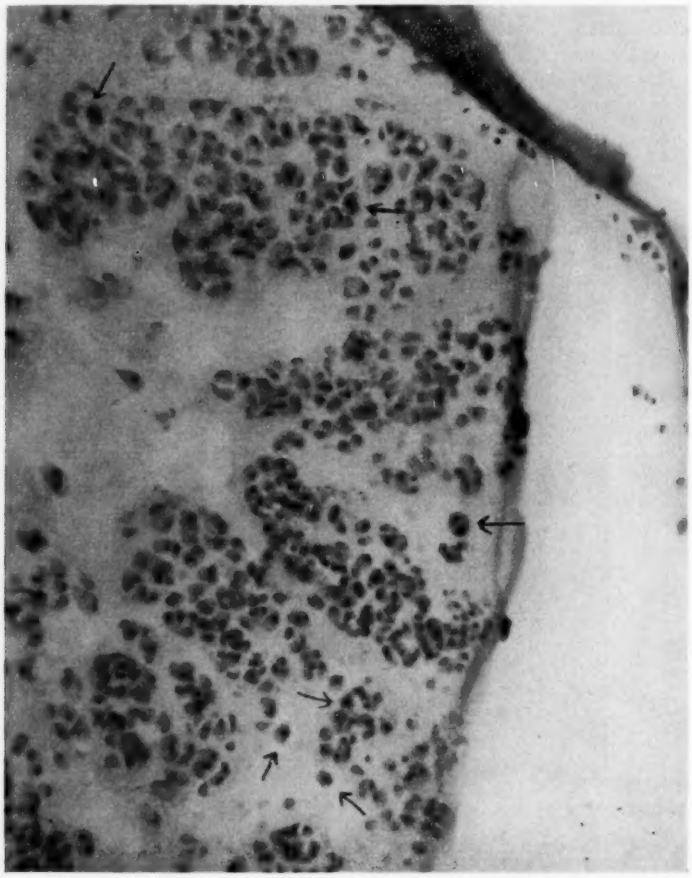

Fig. 2.—The photomicrograph of the chondroma was made from tissue removed at the last conservative operation and shows the large number of cartilage cells, their variation in size and shape, and their clumping together. Arrows indicate some of the mitoses, poorly shown because of technical difficulties in preparing thin sections.

though, after search, no mitoses were found in these sections. In other remote areas the cartilage cells were sparse and large. The matrix itself was quite without structure and very abundant in some areas, slightly granular in other areas, and wholly mucinous in others. It was considered myxoid rather than truly myxomatous. Subsequent conservative operations yielded tissue that did not differ microscopically from the first. On no one slide alone could a differential diagnosis between benignity or malignancy be made. However, the variation in size of cells and particularly the presence of the smaller ones with hyperchromatic nuclei inclined us toward considering the tumor as malignant. The constant recurrence of the tumor after multiple operations strengthened us in our conviction.

All subsequent sections examined were similar to the first except those from the last conservative operation before the radical one, when the tumor had become much more cellular, the cells varied more greatly in size and shape, and frequent, rather irregular mitoses appeared (Fig. 2).

In brief, no one or more slides at any time, except for those from the last conservative and final radical operation, gave absolute evidence of the malignancy of this chondroma, a group most difficult for accurate histologic diagnosis. The combination, however, of the sections and the history of recurrence made certain of the local malignancy.

Fig. 3.—Following interscapulothoracic amputation.

CASE 2.—A Caucasian male, aged 62 years, came under our observation on Dec. 1, 1937. His trouble dated back to 1904, at which time he was bitten on the top of the right shoulder by a venomous snake (Queensland death adder) in Australia. A keloid first began to develop in this area in 1912 and was excised in 1913. No further trouble was noticed until 1935 when a swelling developed in the same region for which several applications of radium were administered.

In December, 1937, examination revealed a tumor approximately 2 cm. in diameter situated midway between the clavicle and spine of the scapula on the superior aspect of the right shoulder. There was considerable breaking down of the surrounding superficial tissue, apparently the result of previous irradiation. The patient complained of much pain in the involved area. X-rays of the shoulder showed no bone involvement. A radiograph of the chest revealed no demonstrable metastasis. The first operation was performed on Dec. 7, 1937. As radical a removal of the tumor and adjacent ulcerated area was done as seemed justifiable. This included a portion of the deltoid muscle, a portion of the trapezius muscle, and areas close to the brachial vessels and anterior to the clavicle.

The pathologic report of the removed tissue was "fibrosarcoma of low malignancy." Various sections of the tissue removed from different areas of the operative specimen were described as: "(a) Pure, hard, fibrous keloid, (b) fibroma very

like uterine fibroids, and (c) fibrosarcoma with mucoid type of degeneration but many mitoses.''

From this operation the patient made a good recovery. Examination of the specimens seemed to show adequate removal. The area was later successfully skin-grafted.

A second operation was performed. On July 22, 1938, at a follow-up examination, a small, freely movable nodule approximately 1.5 cm. in diameter was removed just below the outer third of the clavicle. Examination of the tissue elicited the following report: ''Tissue: Recurrent fibrosarcoma. Tissue looks rather mature, ripe, and relatively benign, closely resembling keloid, but there are many mitoses present.'' Shortly thereafter another nodule was seen to be developing just lateral to the one described. At this point it was decided that the patient should be given the benefit of consultation, particularly as related to irradiation. He was referred to Dr. Edwin I. Bartlett, of San Francisco, whose opinion and treatment are briefly recorded as follows:

After examining the patient and reviewing the microscopic slides submitted in consultation with x-ray and pathologic chiefs at the University of California Hospital, it was decided that the situation looked serious but that surgery followed by irradiation seemed justifiable. It was felt that the lesion was a sarcoma of high local virulence but of low grade as far as metastasis was concerned.

At operation a large nodule was found attached to the clavicle, and another mass of tumor was found beneath the clavicle and adherent to it at the site of the previous operation. All the involved tissue was removed with wide margin and was packed down to the fossa behind the clavicle, so as to leave exposed the area of deepest recurrence.

A subsequent communication from Dr. Bartlett read as follows: ''I warned Mr. — that we could not guarantee against a future recurrence and that time only would tell. He seemed to understand the situation thoroughly but felt as I did that after Dr. Taussig's rather strenuous treatment with radium the chances of recurrence were reduced to a minimum.''

The patient returned to our care on Sept. 22, 1938. A fourth operation was performed on Oct. 5, 1938. He was again subjected to operation because of the appearance of a tumor just beneath the outer third of the clavicle. The tumor, which was approximately 2 cm. in diameter, was found lying beneath and in the pectoralis major muscle. It was attached to, but apparently not involving, the under surface of the clavicle. Due to its intimate contact with the brachial plexus and associated vessels, complete gross removal of the tumor seemed doubtful. Eight 2 mg. tubes of radium were packed into the edges of the wound and allowed to remain for forty-eight hours.

A fifth operation was performed on Dec. 14, 1938. A recurrence had taken place above the clavicle a little medial to its midportion. This could be only inadequately removed because of its adherence to the brachial vessels. Ten 1 mg. tubes of radium were implanted around the edge of the wound and allowed to remain for forty-eight hours.

Pathologic Report.—Tissue removed at the primary operation and the two subsequent conservative ones showed, in histologic preparations, a remarkable similarity, the same spindle-shaped cells in bands and whorls and the whole section quite homogeneous and not unduly vascular. The earlier sections contained few or no mitoses. The sections from this last conservative operation showed again a similar picture save that very many mitoses were now present, even though they were small, compact, and not outstandingly irregular (Fig. 5).

Subsequent recurrences took place in the regions previously described, and at Dr. Bartlett's suggestion these were injected with cystine hydrochloride, according to the technique as described by Dr. Jesse L. Carr. They apparently were not enthusiastic about the results to be expected but had noted some encouraging results.

One hundred milligrams of cystine hydrochloride were dissolved in 2 c.c. of freshly boiled water and injected immediately into the center of the recurrence. Seven such injections were given without apparent benefit.

Fig. 4 taken at this time shows an ulcerated area containing a recurrence above the clavicle and two prominences below the clavicle, seats of other recurrences.

At this time it was felt that all of the possibilities of conservative treatment had been exhausted and that any hope of cure lay in interscapulothoracic amputation. Repeated examinations revealed no demonstrable evidences of metastasis.

On Feb. 25, 1939, Dr. Bartlett was again appealed to, and he kindly wrote:

"We are still of the opinion that there is a sarcoma of high local virulence but of low grade as far as metastasis is concerned.

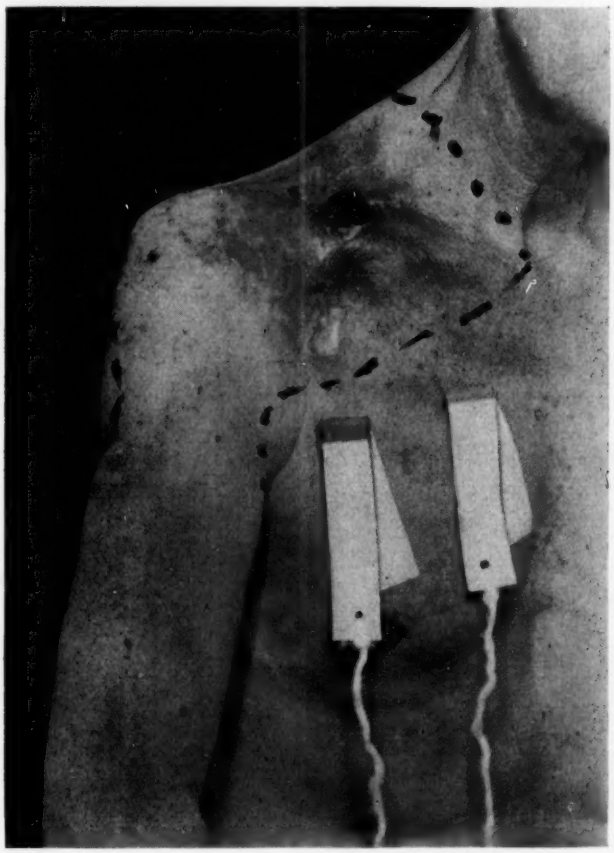

Fig. 4.—Showing recurrences along clavicle and outline of incision.

"In the event, therefore, that we can be reasonably certain that there can be no metastasis by thorough x-ray examinations we are faced with removal of the arm and shoulder girdle to save the life of a patient who is already not young, or the other alternative of continuing as in the past until such time when metastasis occurs.

"While a shoulder girdle amputation is a big piece of surgery and carries with it a certain degree of shock, I feel that Mr. — could safely embark on such a procedure. As to mutilation, there is nothing much more severe, but he can be fitted with a shoulder apparatus which will carry his clothes just as well as the real shoulder."

A sixth operation, interscapulothoracic amputation, was performed on March 7, 1939. Incision was made as shown by the tracing in Fig. 4. In order to determine

whether or not the condition was operable, the clavicle was first disarticulated at its sternal attachment and the incision carried back across the base of the neck and to the chest wall by severing the upper medial portion of the pectoralis major muscle. Opportunity was afforded by lifting the clavicle to explore the structures beneath. This maneuver was considerably handicapped as a result of much scar tissue formation from previous operative trauma and irradiation. There being no evidence of extension of the lesion to these areas, the operation was performed. The subclavian vein was ligated first; the anterior scalenus muscle was then severed after isolating and protecting the phrenic nerve; this gave adequate exposure of the subclavian artery which was then ligated. It does not seem necessary to describe in detail the

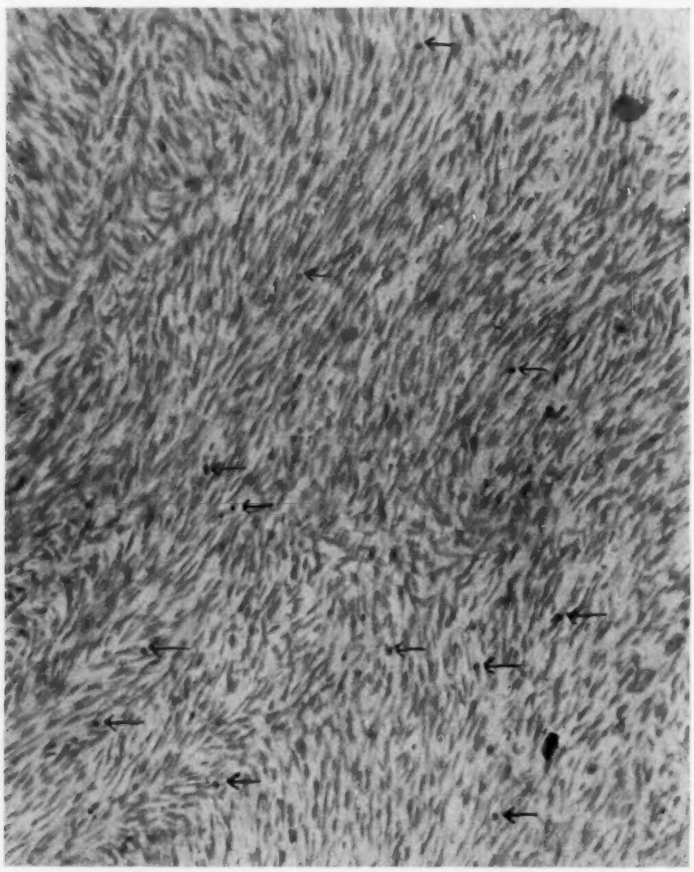

Fig. 5.—The photomicrograph of the fibrosarcoma was made from tissue removed at the last conservative operation and shows the homogeneity of its structure, the spindle cells arranged in bands and whorls, their similarity in size and shape, and the avascularity. Arrows indicate the very numerous, but rather normal, small mitoses and pyknotic nuclei.

operation of interscapulothoracic amputation since this has been adequately covered by many standard treatises on this subject. It would seem, however, that an approach such as the one described permits the control of the vascular supply to the operative field from the start and also enables one to explore the regions which, if involved, would render proceeding with the operation inadvisable. Littlewood[2] advocates an approach from the back. At this particular operation a rather large skin flap from the axilla and inner aspect of the arm was preserved in order to cover the large defect. The patient stood the operation well, being given a transfusion at its completion.

A somewhat complicated convalescence ensued due to the fact that the patient developed an acute cholecystitis requiring operation.

The examination of the removed specimen revealed, in addition to the involvement previously described, a nodule of tumor tissue the size of an English walnut lying directly beneath the clavicle and intimately associated with the brachial vessels. The excision lines seemed adequate. To date, the patient is well, back at his former occupation, and without evidence of recurrence.

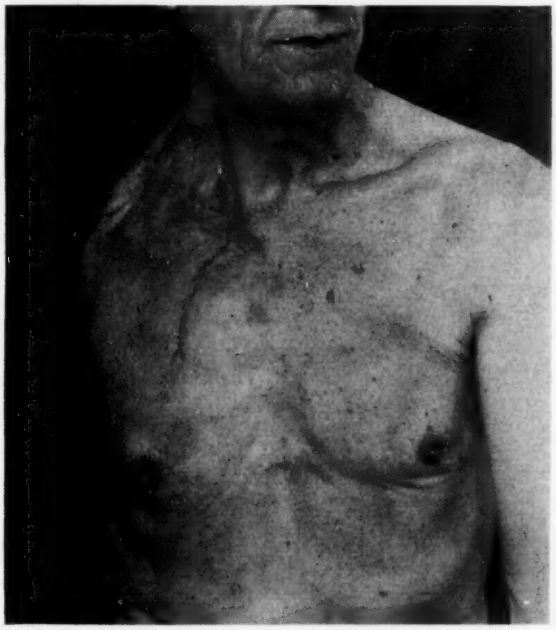

Fig. 6.—Following interscapulothoracic amputation.

Fig. 7.—Simple appliance to preserve contour of shoulder.

SUMMARY

Two persons upon whom successful interscapulothoracic amputations have been performed are reported. They suffered from conditions which we believe most frequently justify the operation under discussion; namely, patients suffering from locally malignant and recurring tumors, not prone to metastasize, so situated that they cannot be effectively removed locally because of their close proximity to structures important to the arm.

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METASTASES IN THE SKULL FROM CARCINOMA OF THE THYROID

A Clinical and Roentgenographic Study of Two Cases With a Brief Survey of the Literature

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BULKY soft tissue tumors which involve the skull are not very common and when seen usually present a problem in differential diagnosis. The tendency for thyroid carcinomas to metastasize to the skull is recognized generally. However, the insidious character of the primary growth, the long latent period which often supervenes between the recognition of the primary growth and its secondary manifestations, and the unusual characteristics of the secondary tumor in the skull often make the diagnosis difficult.

LITERATURE

The incidence of carcinoma of the thyroid, as given by different writers, varies between 0.5 and 2 per cent of all thyroid disease. Hare and Swinton[1] found primary malignant disease of the thyroid to be present in 2.4 per cent of the cases in a series of 15,522 thyroid operations on 12,946 patients at the Lahey Clinic. In the series of almost 17,000 thyroidectomies reported by Crile and his associates,[2] malignant disease was present in approximately 2 per cent. Metastases from carcinoma of the thyroid are found most frequently in the lungs. The combined figures of Pemberton,[3] Ehrhardt,[4] and Dinsmore and Hicken,[5] give an average incidence of 31 per cent pulmonary metastases in a total of 940 cases. In Pemberton's series of 438 cases there was metastasis to the lungs in 24 per cent, while Ehrhardt[4] reported metastasis to the lungs in 54 per cent of 238 cases of all types of malignant goiter. Dinsmore and Hicken[5] found pulmonary metastasis in 14 per cent of 264 cases.

Despite the higher frequency of pulmonary metastasis, most attention has been directed toward the skeletal system as the site of secondary growths. Carcinomas of the thyroid, along with carcinomas of the breast and prostate, have a striking tendency to metastasize to bone. The special interest in the skeletal system is due probably to the relatively high incidence of involvement and to the fact that a secondary growth in bone may be the first indication of malignant disease in the thyroid gland. Dinsmore and Hicken[5] were able to find in the literature

Received for publication, April 27, 1940.

223 cases of bone metastases from malignant goiter. These writers found that 6 per cent of their 264 cases of malignant thyroid disease metastasized to bone or 18 out of 124 cases in which metastases were present. Pemberton[3] also found 6 per cent of his 438 cases of malignant thyroid disease had secondary growths in the skeletal system.

The predilection for secondary thyroid carcinoma to involve certain of the bones of the skeletal system has been recognized for some time. While the metastatic lesions are occasionally single, in most instances there are multiple foci with involvement of several organs or systems. According to Ewing,[6] the metastases generally appear first near the cranial sutures in the skull or in the region of the epiphyses in the long bones. The most frequent sites of localization within the skeletal system are the skull, vertebrae, and pelvis. Deposits are also commonly found in the sternum, mandible, femur, clavicle, and ribs. The subject has been reviewed by several writers, notably Joll,[7] Simpson,[8] and Ginsburg.[9]

Metastatic lesions to the skull occasionally appear as an isolated lesion, but the metastatic process is usually more widespread. Many of these metastatic lesions exhibit pulsations synchronous with the arterial pulse and may be mistaken for aneurysms. Crile[10] has recently reported four such lesions of the sternum and reviewed the literature upon the subject.

One of the first pulsating tumors of this sort to be reported was that of Morris.[11] In this case a large parietal lesion developed and later began to pulsate before multiple metastatic lesions became apparent in the skeletal system. The early literature contains several reports of bulky metastatic tumors of thyroid origin in the skull. Haward's[12] case had a large pulsating tumor in the skull as well as in the left scapula and iliac bone. Death in that instance was due to the cranial lesion which had reached sufficient size to cause compression of the brain. Wölfer's[13] case was of a rapidly growing frontal lesion which was associated with enlargement of the left lobe of the thyroid. A similar case was reported by Cramer.[14] Kanoky[15] in 1916 reported a case in which a metastatic tumor arose in the left temporal region. At death it was found that the growth was attached to the dura and had displaced fully one-third of the contents of the left side of the cranial cavity. Recently Connell[16] has reported two cases of massive metastatic tumor to the skull. In his first case there was no biopsy of either the primary or secondary growth and the diagnosis was made clinically. A biopsy of the cranial tumor in the second case was diagnosed as adenocarcinoma subsequent to fetal adenoma, the diagnosis of carcinoma having been made chiefly from the metastatic nature of the tumor. The growth had destroyed the outer table and most of the inner table of the occipital region of the skull. Williamson[17] has reported a similar case in which the skull was the site of three large growths which had destroyed much of the underlying bone. Although there was no biopsy of either the

primary or secondary growths, the thyroid gland was markedly enlarged. In both of Connell's cases there was a palpable mass in the thyroid gland. None of the cases reported by these two authors exhibited pulsation.

Pathology.—It is generally recognized that carcinomas of the thyroid may exhibit few histologic evidences of malignancy, either in the primary or secondary growths. Müller[18] in 1871 was apparently the first to note the tendency for metastatic lesions of the thyroid to appear microscopically benign. The much quoted case of Cohnheim[19] in which a "benign adenoma" of the thyroid metastasized to bone has been reviewed by several writers[5, 8] and it is generally agreed that the tumor in question showed definite evidence of malignancy. The concept that "benign adenomas" of the thyroid can give rise to distant and widespread metastases has gained favor with some writers. Joll[7] accepted this view and collected from the literature forty-three cases in which bone metastases were associated with a "normal thyroid or benign goiter" and added another of his own. Kanoky,[15] in reviewing the literature from the standpoint of nonpulsating tumors of the skull, also accepted this concept. Similarly, Ginsburg,[9] in a study of bone metastases in thyroid tumors, concluded: "Bone metastasis is of frequent occurrence not only in carcinoma and sarcoma but also in simple adenoma of the thyroid gland."

Many writers, however, especially those who have studied the problem more recently, do not accept such an entity as the benign metastasizing adenoma or goiter. Simpson[8] carefully reviewed the literature and came to the conclusion that there is no "benign metastasizing goiter." Similarly, Dinsmore and Hicken[5] were led to conclude that the so-called benign metastasizing adenomas are malignant lesions and agree with Simpson that the term is misleading and should be abandoned. Graham[20, 21] emphasizes the careful study of the tumor for local evidence of malignancy and states that in his cases in every instance in which metastasis has occurred from a malignant adenoma blood vessel invasion has been noted. In a study of four cases of malignant adenoma of the thyroid with local recurrences in the veins of the neck, Graham[22] states: "In none of the cases was the tumor as a whole frankly carcinomatous from a purely histological standpoint. . . . The pathologist as well as the clinician at the time of the primary operation had difficulty in making a positive diagnosis of malignancy." On this basis Crile and Crile, Jr.,[23] have advocated radical resection of the neck veins in cases of malignant tumors of the thyroid gland.

REPORT OF CASES

CASE 1.—A 41-year-old white woman was first admitted to the hospital in February, 1931, with the complaints of enlargement of the right side of the neck and a swelling on the head. In the spring of 1930 she had first noticed a hard, painless lump in the right side of the neck. The following summer the patient

developed a painless swelling in the left frontoparietal region, which gradually increased in size, but the patient did not consult a doctor until about ten months previous to hospital admission. The past history was essentially noncontributory. There had been no cranial trauma, night sweats, palpitation, or weight loss.

The positive physical findings at the time of admission were limited essentially to the head and neck. The right lobe of the thyroid was considerably enlarged. The portion of the lobe which was adjacent to the trachea was of stony hardness and fixed to the contiguous structures, while the remaining tissue was soft and diffusely enlarged. The gland did not pulsate and no bruit could be heard. Laryngoscopic examination revealed a normal larynx with no evidence of vocal cord paralysis.

In the left frontoparietal region was a pulsating tumor which measured 4 by 1.5 cm. The mass was fixed to the underlying structures and, although the pulsations were synchronous with the heart beat, no bruit could be heard. Neurologic examination gave normal results. The basal metabolic rate was plus 10 per cent.

Stereoroentgenograms of the skull showed an area of bone rarefaction in the left frontoparietal region which measured 4.5 by 4 cm. (Fig. 1). Films taken with the rays tangential to this area demonstrated a thinning of both tables of the skull with a suggestion of radiating bony spicules. The defect had slightly irregular borders but was fairly sharp in definition. The surrounding bone was the seat of slight sclerosis.

The clinical diagnosis was carcinoma of the thyroid with metastasis to the skull. A right thyroid lobectomy was performed from which the patient made an uneventful recovery.

Following operation the patient received x-ray therapy to the tumor mass in the skull. During the succeeding nine months the size of the growth increased to 6 by 7 by 2 cm. It was tender at the base, firm, but not hard and was fixed to the skull but not to the overlying skin. Auscultation revealed no bruit and it had ceased to pulsate. Neurologic examination was normal and the only complaint at the time was that of severe headache. Roentgenograms of the skull at this time showed marked increase in the extent of bone destruction (Fig. 2). The defect measured 8 by 4.5 cm. and the involved bone appeared to have been almost completely destroyed. There was involvement of the temporal region which had not been seen on the previous films. The bone adjacent to the area involved by the tumor showed a more marked sclerosis than previously. There was no evidence of increased intracranial pressure.

At operation the tumor was found to have penetrated the skull and become adherent to the underlying dura. The tumor surrounding calvarium and upper leaf of the attached dura were removed. The patient made an uneventful recovery and was discharged from the hospital on the thirteenth postoperative day.

One year later the complaint of abdominal pain led to the discovery of an enlarged and tender liver. Subsequent examinations revealed progressive nodular enlargement of the liver. Her course was progressively downhill; she lost weight, developed a marked anemia, and became cachectic. At her last visit, three years after removal of the metastatic lesion in the skull, there was a nodule 2 cm. in diameter at the posteroinferior margin of the temporal bone defect. There were a number of enlarged and firm lymph nodes in the cervical chain. The patient died in December, 1934. Autopsy was not obtained.

Pathology.—The right lobe of the thyroid removed at operation measured 8 by 8 by 4 cm. While the greater portion of the gland was composed of firm yellow-brown tissue, the upper pole contained a circumscribed nodule 4 cm. in diameter. This nodule contained cartilage and bone, while several small adjacent nodules appeared to be composed of normal thyroid tissue. The capsule of the gland was everywhere intact.

Microscopically, the greater portion of the lobe consisted of clusters and cords of cells of variable size, shape, and staining qualities. In some areas there were cystic spaces filled with colloid. Many dilated capillaries were present between the cell clusters and some of these showed evidence of invasion by the adjacent tumor tissue. Invasion of the fibrous trabeculae which formed part of the stroma of the

Fig. 1.

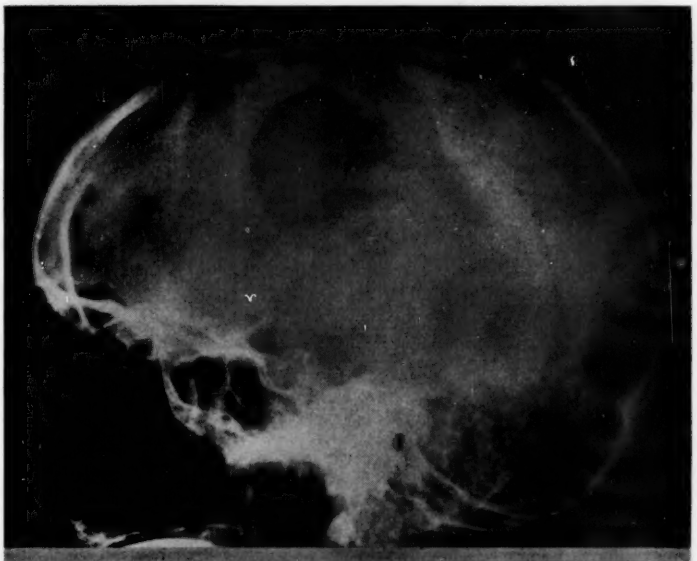

Fig. 2.

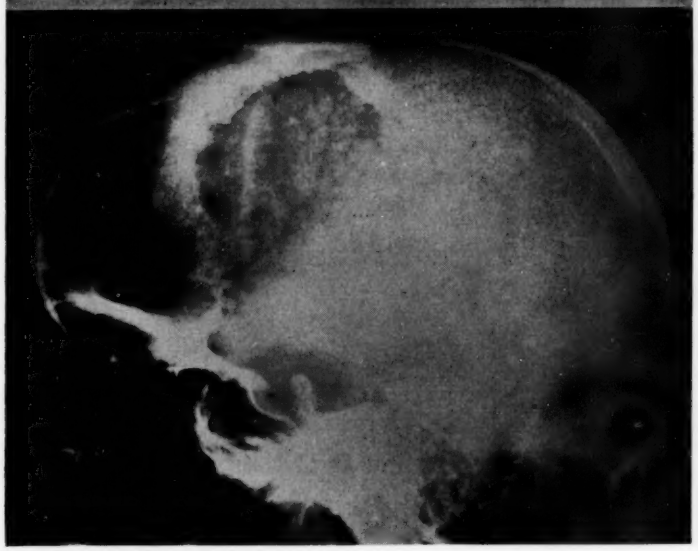

Fig. 1.—Case 1. Roentgenogram taken at the time of admission.
Fig. 2.—Case 1. Roentgenogram taken about nine months after admission. Note increase in size of the defect despite local x-ray therapy.

growth was also present in many places. The large nodule at the upper pole of the lobe was composed of dense fibrous tissue, acini filled with colloid, and foci of calcification. Sections through the smaller nodules revealed normal thyroid tissue. The pathologic diagnosis was carcinoma of the thyroid gland.

The tumor with adjacent calvarium removed from the parietal region of the skull measured 9 by 8 by 5.5 cm. Grossly, the tumor tissue had an opaque, yellow appearance and contained many large, intercommunicating cysts filled with transparent,

mucilaginous material which resembled colloid. (Fig. 3.) There was complete destruction of the involved calvarium aside from a few small fragments of bone within the tumor. The growth, which projected about 2 cm. into the cranial cavity, was firmly adherent to the outer leaf of the dura.

Fig. 3.

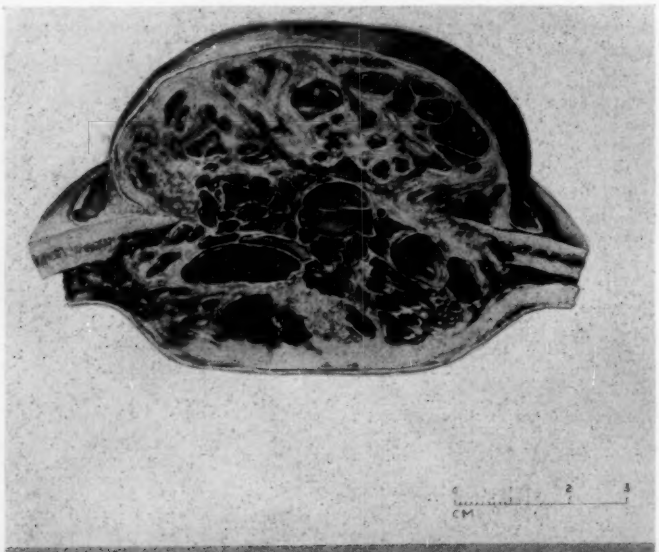

Fig. 4.

Fig. 3.—Case 1. Drawing of the specimen removed at operation. The specimen includes the tumor, adjacent calvarium, and outer leaf of the dura to which the growth is adherent.

Fig. 4.—Case 1. Photomicrograph of the more cellular portion of the tumor in the calvarium. Note the cell cords separated by thin strands of connective tissue. (Hematoxylin and eosin, ×250, green filter.)

Microscopically, the tumor was very cellular, being composed of cells with large, round, pale nuclei and vacuolated cytoplasm with indistinct cytoplasmic outlines. The cells lay in a loose connective tissue stroma and showed a distinct tendency toward acini formation. Many of the acini were dilated and filled with colloid. The latter was present as well in the reticular stroma of the tumor. There was no histologic evidence of invasion of either the periosteum or dura,

although tumor thrombi could be observed in many of the smaller vessels. Only an occasional mitotic figure was observed. The pathologic diagnosis was metastatic carcinoma of the thyroid in the calvarium. (Fig. 4.)

The clinical diagnosis in this case was fairly obvious since both primary and metastatic lesions were demonstrable. A two-year interval between the first and subsequent metastases and a three-and-one-half-year survival following the appearance of the first metastatic lesion suggests that the tumor was not highly malignant. It is significant that symptoms of cerebral compression were absent despite the rapid growth of the metastatic lesion and the large size it had attained at the time of removal. Although the growth had become adherent to the dura, the latter proved to be rather resistant to invasion by the tumor.

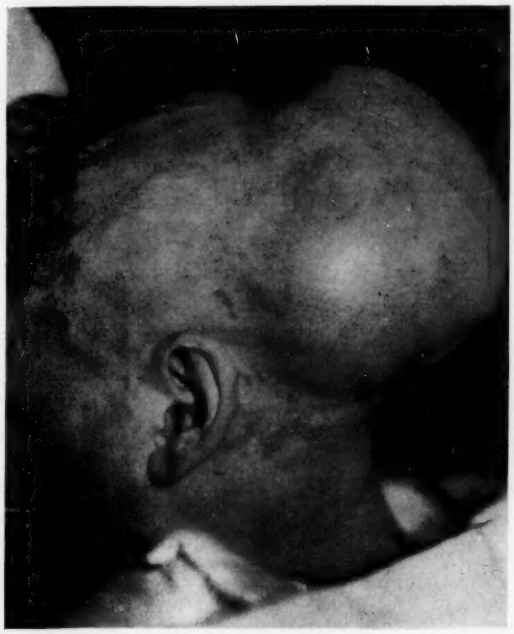

Fig. 5.—Case 2. Photograph of the tumor which presented over the left parietal and occipital region but involved the right side as well.

CASE 2.—A 50-year-old white woman was first seen in September, 1934, with the complaint of a swelling on the back of the head of eight years' duration. About eight years previously she had been struck over the left parietal region with a heavy brass curtain rod. She was not unconscious and had no subsequent symptoms other than a slight "dent" and slight tenderness in this region. During the following year there slowly developed a small tumor about 1 to 2 cm. in diameter at the site of the trauma. Although the tumor had slowly increased in size during the first three years, in the following three years it had doubled in size. In June, 1934, the patient suffered several episodes of hematuria associated with pain which began in the left costovertebral angle and radiated anteriorly.

At the age of 14 years the patient had a goiter. This reappeared with each of her subsequent four pregnancies but had also subsided during the puerperium.

However,' following the last pregnancy the enlargement persisted and was removed by a right thyroid lobectomy in 1921.

Examination revealed a large, pulsating, soft tumor over the posterior parietal and occipital region. This involved the entire left side but extended beyond the midline to include the right as well (Fig. 5). The pulsations were synchronous with the radial pulse and a soft bruit could be heard. The tumor was firmly attached to the underlying calvarium but did not appear to involve the scalp. There was visible distention of the superficial temporal and angular veins on both sides of the head. Neurologic examination gave normal results.

Roentgenograms of the skull at various stages in the development of the tumor were available. Films taken in June, 1929, about three years after the local injury, disclosed a destructive lesion in the left parietooccipital region which measured about 5.5 by 3 cm. (Fig. 6). The defect was irregular in outline but moderately well demarcated. Anteroposterior views of this region disclosed the lesion to consist of marked rarefaction of both tables of the calvarium with almost complete destruction of the bone in some areas. The region involved by the growth as well as the rest of the skull showed accentuation of the vascular markings.

Films taken in August, 1934, showed marked extension of the lesion to form a defect without evidence of osseous structure which involved the entire left occipitoparietal region and extended beyond the midline to the right (Fig. 7). At this time it measured 8 by 10 cm. in its two greatest diameters. The contour of the defect was rather irregular, but the adjacent bone showed no unusual characteristics. In this region and throughout the skull the vascular markings were very prominent. There was no demonstrable intracranial calcification and no evidence of increased intracranial pressure.

The impression was a metastatic malignant tumor of the skull, although the possibility that the growth might be either a meningioma or a vascular tumor of the skull was also considered. The patient entered the hospital in March, 1935, for further study. At this time the growth measured about 12 by 10 cm.

Further investigation of the previous thyroidectomy disclosed that the tissue removed at that time was regarded microscopically as a fetal adenoma. Repeat films of the skull on admission disclosed but little enlargement of the destructive process as compared with the size of the lesion in August, 1934. The borders of the defect were quite irregular and showed moderate sclerosis. Roentgenograms of the pelvis revealed a large destructive lesion in the right iliac wing with involvement of the inferior segments of the coccyx and entire sacrum. The clinical diagnosis was carcinoma of the thyroid with metastasis to the skull, pelvis, coccyx, and kidneys.

It was decided to remove the growth from the skull. At operation the tumor proved to be exceedingly vascular and after reflecting the scalp and encircling the bone adjacent to the tumor the remainder of the procedure was postponed for another session. At the second operation the tumor was found to have a wide attachment to the underlying dura. During the process of elevating the bone flap, this pedicle was broken across and the ensuing hemorrhage could not be controlled. In spite of a transfusion of 2,000 c.c. of blood the patient expired.

Pathology.—The tumor with several small pieces of calvarium removed at operation weighed 458 Gm. after fixation in 10 per cent formalin. The growth itself measured 12.5 by 10 by 6.5 cm. and had a fleshy consistency with the gross characteristics of normal thyroid tissue. The rim of calvarium about the tumor showed obvious invasion by the neoplastic tissue.

At autopsy, only a small portion of the right lobe of the thyroid was present. This was uniformly light pink in color and, although it was closely adherent to the

trachea, there was no gross evidence of invasion. The left lobe of the gland appeared normal. The positive autopsy findings were limited to the brain, pelvis, and kidneys. At the site of the operative wound there was a pedunculated mass of tumor tissue adherent to the dura. This measured 5 cm. in diameter and had a

Fig. 6.

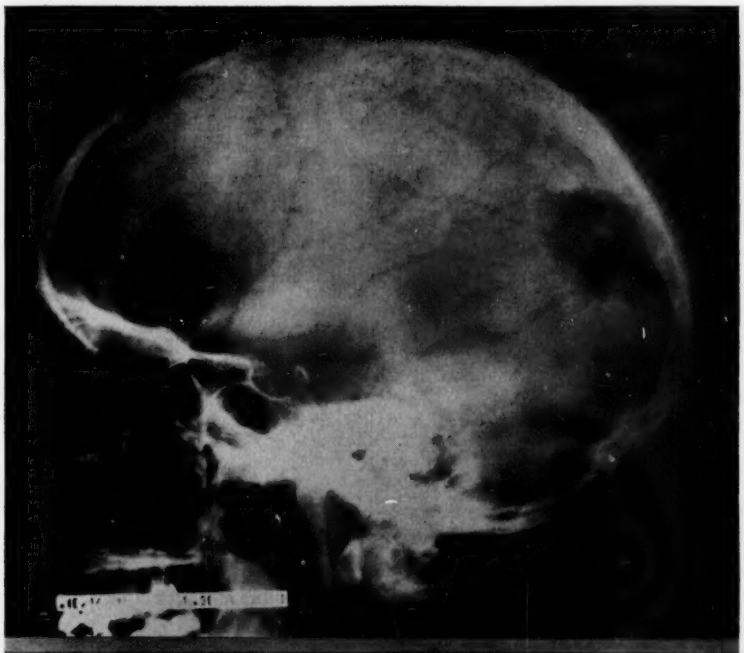

Fig. 7.

Fig. 6.—Case 2. Roentgenogram taken about three years after the local injury and about five years before admission.

Fig. 7.—Case 2. Roentgenogram taken about five years after that shown in Fig. 6 and at the same time as that shown in Fig. 5. Note the widespread involvement and the complete destruction of both tables of the skull.

gross appearance identical with that of the tumor described above. The calvarium at the operative site measured 1 cm. in thickness. Although there was no intradural extension of the tumor, there was marked compression of the left occipital lobe of the brain with definite cerebellar herniation.

Both kidneys were the site of multiple tumor nodules, the largest of which measured 5 cm. in diameter. These nodules were fairly firm, had a light pink color and a smooth, collagenous-appearing cut surface. Tumor tissue of the same character was present in the bones of the pelvis and a mass about 4 cm. in diameter involved the coccyx.

Microscopically the tumor removed from the calvarium varied little from that of normal thyroid tissue. It was composed of acini which showed moderate variation in size and type of epithelial lining. The larger acini were lined by flattened epithelium and contained an abundance of grayish pink staining colloid. Some of the smaller acini had no content and were lined by high cuboidal or columnar epithelium. There was no interacinar colloid, no lymphocytic infiltration, and nowhere did the epithelium present more than a single layer of cells. No mitotic figures were observed. There was invasion of the adjacent calvarium and dura. Occasional foci of new bone formation were present.

The microscopic appearance of the small nodule of thyroid tissue remaining from the previous lobectomy was essentially as above. Mitotic figures were not observed and there was no invasion of the trachea.

The tumor in the kidneys closely resembled thyroid tissue of the fetal type. The majority of the acini were small and contained no colloid although some had a moderate amount of colloid and appeared not unlike normal thyroid tissue. There were no mitotic figures and no epithelial infoldings. There was some tendency toward a radial arrangement of acini about blood vessels which were numerous and large. The growths were fairly well circumscribed and compressed the adjacent renal tissue.

Microscopically, the tumor in the coccyx showed invasion of the spongy bone and complete filling of the marrow spaces. In many places the tissue was comparable to that in the kidneys, but in other places there was more obvious evidence of malignancy. In these latter areas there was little tendency toward the formation of acini and colloid material was seen lying loose in the intercellular tissues. The cells appeared less differentiated and of the more rapidly growing type. The final diagnosis was carcinoma of the thyroid with metastases to the kidneys, bones of the skull, pelvis, and coccyx.

The five-year interval between the thyroidectomy and the first indication of a metastatic lesion serve to emphasize the insidious character of malignant disease of the thyroid gland. Despite the fact that at autopsy the left lobe of the thyroid and the remaining remnant of the right lobe showed little histologic evidence of malignancy, the several metastatic lesions showed considerable variation in microscopic pictures. Thus, the tumor tissue invading the pelvis and coccyx had all the characteristics of carcinoma while that in the calvarium resembled normal thyroid. Metastatic lesions from a malignant thyroid, particularly those arising from a "malignant adenoma," may show either more or less histologic evidence of malignancy than does the primary growth. Thus, despite the histologic character of the tissue, the ability to give rise to distant metastases and the destructive and invasive character of these brands the primary growth as carcinoma.

DISCUSSION

Grossly and roentgenologically the lesions in both cases presented many similar characteristics. Both lesions were destructive from the onset and gave rise to minimal peripheral bone reaction in the later stages of the process. This bone reaction was more pronounced in the second case where the destructive lesion had progressed to a more advanced stage. Both lesions were highly vascular as evidenced in the roentgenograms by the accentuated vascular markings about the lesion as well as throughout the remainder of the skull. This increased vascularity was largely venous, being due for the most part to the greatly enlarged sinuses. The enlargement of the angular and superficial temporal vessels and the necessity of a two-stage procedure in the second case demonstrates the associated vascularity of the overlying soft tissues.

Although there are several types of primary growths which produce destruction of the calvarium, only a few need be considered here. Meningiomas in some instances may cause local erosion of bone and proliferation of the adjacent bony structures, but the destruction of osseous tissue is rarely very great. The defect in the skull is usually quite irregular and associated with local increase in vascularity. Rarely perforation of the skull may give rise to large soft tissue tumors. An unusual case of this type was described recently by Davidoff.[24]

The hemangiomas of bone have been studied by Bucy and Capp.[25] A high percentage of these tumors involve either the vertebrae or the skull. The tumor may be present as a bony, hard, elevated area or there may be a central portion which is soft and pulsating. The characteristic x-ray appearance is the presence of large "sunburst" trabeculations and spicules radiating out from the plane of the bone. The cortex of the bone is frequently destroyed, but the periosteum remains unbroken, though it may be greatly expanded.

Osteogenic sarcomas are not common lesions in the skull and are characterized by destruction of bone, invasion of periosteum and soft tissues and often by the presence of radiating spicules of bone. These tumors are rapidly growing and even in the early stages there is definite loss of bone by x-ray. According to Dyke,[26] primary sarcoma of the skull closely simulates the bone reaction produced by meningiomas but shows more bone destruction and less vascularity.

The writers are indebted to Dr. A. W. Oughterson for permission to use his records, to Dr. Hugh Wilson for the roentgenograms, and to Dr. Harry Zimmerman for the use of the pathologic material.

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URINARY STONES

A Study of Their Etiology in Small Children in Syria

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CALCULOUS DISEASE is now understood to be a symptom rather than a disease entity. Some factors in the causation of stones are known, but there are still many cases in which the etiology is obscure. Confusion arises from the grouping together of cases which really belong in separate classes. One group of cases should be of special interest because of the absence of common known factors; viz., young children with bladder stones, with no obstruction, no foreign body, and no known infection. This condition is not uncommon in the southern countries of Asia.[2, 9, 14, 20] It was common in children in Europe during the early part of the last century. It seems that there has been some change in the mode of life which has reduced the incidence.[7, 9] Perhaps this change is now taking place in the Orient. Does not this situation present ideal conditions for the study of the human stone problem in its simplest form? The relatively short life histories of these patients should reduce the possibilities of error with respect to etiological factors.

This paper will summarize an investigation at the American Presbyterian Hospital, Tripoli, Republic of Lebanon, Syria, during the years 1931 to 1934.

Age.—The occurrence of solitary bladder stones during the first few years of life seems to indicate that these cases represent a disease which begins in infancy or very early childhood (Table I). Children come to operation for bladder stones many months or years after the onset of symptoms. At the time of operation the patient has probably long since recovered from the condition which caused the stone. Recurrences are rare.

Sex.—All the literature points to the relative infrequency of bladder calculi in girls. The series of 41 cases in Syria consisted of 39 boys and 2 girls. The obvious explanation is that the female urethra is larger and more patulous and passes stones more easily. It seems probable that many are passed silently in both sexes.[10] Stone formation may be equal in the two sexes, but the patients that come for treatment are nearly all male.

Climate.—The aridity of the climate offers a plausible explanation; perspiration is profuse and thirst may be unduly prolonged. It has been suggested that the present geographical distribution of bladder calculi in children corresponds roughly to those areas where the camel

Received for publication, April 22, 1940.

TABLE I*

AGES OF 41 CHILDREN OPERATED UPON FOR BLADDER STONE IN SYRIA

AGE	NO. OF CASES	
1	4	
2	5	Three-fourths of cases during the first seven years of life
3	5	
4	6	
5	5	
6	5	
7	0	
8	3	
9	3	
10	1	
11	1	
12	1	
13	1	
14	1	
Total	41	

*This table includes our cases and those of Ellis Herndon Hudson, formerly of Deir ez Zore, Syria; Waheeb Nini, of Tripoli, Syria; and Ernest Wyder, of Nazareth, Palestine.

is used as a beast of burden. In our cases the onset of symptoms was more often in the dry hot months of spring and summer (Table II).

TABLE II

SEASON OF ONSET OF STONE SYMPTOMS IN 14 CHILDREN IN SYRIA

MONTH	NO. OF CASES	
January	1	
February	0	
March	1	
April	2	Two-thirds of cases during four bright hot months of spring and summer
May	2	
June	2	
July	3	
August	1	
September	0	
October	1	
November	1	
December	0	

However, study of individual cases did not indicate that stone formation was the result of dehydration. Furthermore, this theory does not fully explain why stones were more frequent in Europe a century ago.

The distribution of our cases corresponds roughly to the area from which all of our hospital patients came; in other words, along the Mediterranean coast, in the Lebanon Mountain villages, in the inland cities along the Orontes River, on the agricultural plateaus, and in the desert. There is nothing to indicate that any part of Syria is exempt.

Heredity.—The various race groups of this part of Syria are all represented in our small series. There were no Europeans or Americans with lithiasis, but these are a very small part of the population. A

family history of stone can sometimes be elicited, but it should be remembered that in these old countries the family environment is usually unchanged from generation to generation.

Cases have been reported of stones in small children associated with congenital obstruction of the bladder outlet, with congenital atony, and with diverticula. Our cases do not fall into this category; simple removal of the stone effected cure.

The cystine diathesis[4] is certainly an hereditary condition, but none of our cases had cystine calculi. Some writers have assumed that a so-called uric acid diathesis is responsible in some cases, but we do not know of any definite proof.[18]

Heredity does not seem to be an important factor in the etiology of bladder stones in children, except in cases of congenital anomaly and in the cystine diathesis.

Endocrinopathy.—The stones of hyperparathyroidism are composed of calcium phosphate.[1] In our experience most bladder stones from children are composed of uric acid (Table III).

Infection.—The relative absence of pyuria is a striking feature of the condition we are studying. Immediate closure of the bladder wound after removal of the stone has been reported by many surgeons in various countries.[2, 12, 15, 18, 20] This would not be advisable in the presence of infection. However, it is possible that infection may play an important role in the causation of stone without there being infected urine at the time of operation.

Bilharzia is not found in the areas studied.

Rosenow and Meisser reported the production of urinary calculi by placing streptococci from lithiasis patients in devitalized teeth of dogs.[17] Many of our cases had carious teeth, but our records are not complete enough to compare the incidence with that of the general population.

The various urea-splitting bacteria[5] were not considered seriously as possible causes, because most of the stones analyzed had uric acid centers (Table III).

Five of thirteen cases had definite histories of respiratory infections; in one the onset of bladder symptoms was with an acute common cold, complicated by diarrhea. Three other cases had diarrhea, which may have been secondary to the stone. Many physicians in Syria are of the opinion that calculi are the result of urinary tract infections with bacteria of the colon bacillus group. Bacillary dysentery is indeed a prevalent disease and dysuria is a common symptom during the acute phase of dysentery. Large clumps of pus and shreds of fibrin may be found in the urine of infants suffering with bacillary dysentery. However, there is no correlation of observations. We were unable to obtain a history of dysentery in most of our cases.

TABLE III

CHEMICAL ANALYSES OF STONES PICTURED IN FIGS. 1 AND 2*

DESIGNATION	NUCLEUS	SHELL
A 1	Uric acid-Ca and Mg phosphate	Uric acid-Ca carbonate
2	Uric acid	
3	fibrin-Ca and Mg phosphate	
4	Uric acid	Uric acid-Ca carbonate
5	Uric acid	Uric acid
6	Uric acid	Uric acid
B 1	Uric acid	Uric acid
2	Ca carbonate	Uric acid-Ca carbonate
3	Uric acid	Uric acid-Ca and Mg phosphate
4	Uric acid	Uric acid-Fibrin
5	Uric acid	Uric acid
6	Uric acid	Uric acid
C 1	Uric acid	Uric acid
2	Ca and Mg phosphate	
3	Trace uric acid	
4		
5	Ca and Mg phosphate	
6	Uric acid-Ca and Mg phosphate	
D 1	Ca and Mg phosphate	
2	Ca and Mg phosphate	
3	Ca and Mg phosphate	
4	Uric acid	
5	Uric acid	
6	Uric acid	

*Qualitative methods of analysis were used, following the "schema of Heller."[6]

Leucocytosis increases the amount of uric acid excretion. Uric acid stones are frequent in cases of chronic myelogenous leucemia.[21] Is it possible that the leucocytosis of respiratory infections is a contributing factor in the production of uric acid calculi?

Diet.—Most of the substances that make up the bulk of urinary calculi are influenced by diet.

In Syria this disease is not confined to the poor, for we know of several cases in families that, according to local standards, were considered rich.

It is still a common belief that hardness of drinking water predisposes to stone formation; but stones are quite rare in some districts where the water is very hard and occur where rain water is used for drinking. There seems to be no good reason to implicate the minerals in drinking water and not the plant minerals that are ingested. The fact that the centers of many of these stones are composed of uric acid indicates that the minerals ingested have no direct influence.

Uric acid excretion in the urine ordinarily depends to a large extent upon the nucleoproteins of the diet. Syrian peasants may have no meat to eat for long periods of time, and when they do have meat the whole family usually overeats.

Oxalates were not found in any of the stones analyzed. It is possible that oxalates were present, but not in sufficient quantities to cause ef-

fervescence when heated gently with dilute hydrochloric acid. No typical oxalate stones were found.

Vitamin Deficiency.—Osborne, Mendel, and Perry[16] reported that rats fed on a balanced ration without fat-soluble vitamin developed phosphatic urinary calculi. When butter is substituted for lard in the experiments, stones do not form. McCarrison[13, 14] made extensive similar observations, using the diet of various sections of India in his experiments.

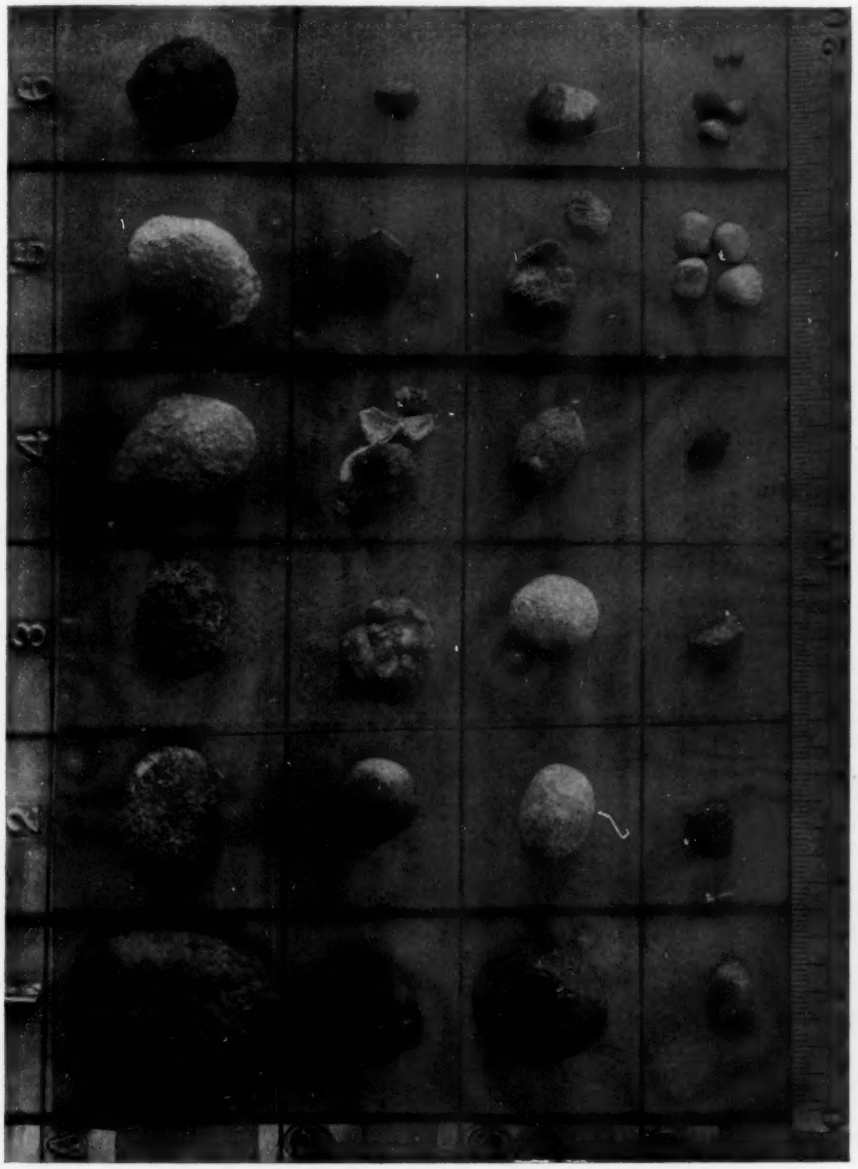

Fig. 1.—Photograph of some bladder stones from children in Syria. A centimeter rule shows the size. *B4* and *C5* were single stones, broken. *C4* proved to be an ordinary peanut with a shell encrusted with common salt, probably substituted by a father who wanted to keep his son's stone. *D5* and *D6* probably have no bearing on this study.

There is little gross similarity between the condition found in rats and that in children. The rats have literally scores of phosphatic stones with infection.[7] Children have solitary stones, without gross evidence

of infection. However, the prime causative factor may not be related to the substance that makes up the bulk of the concretion. It should be remembered that most mammals excrete allantoin instead of uric acid; man, the anthropoid ape, and the Dalmatian coach hound are exceptions to this rule. Uric acid stones are not found in animals,[9] except in experimental animals with Eck fistulas.[5]

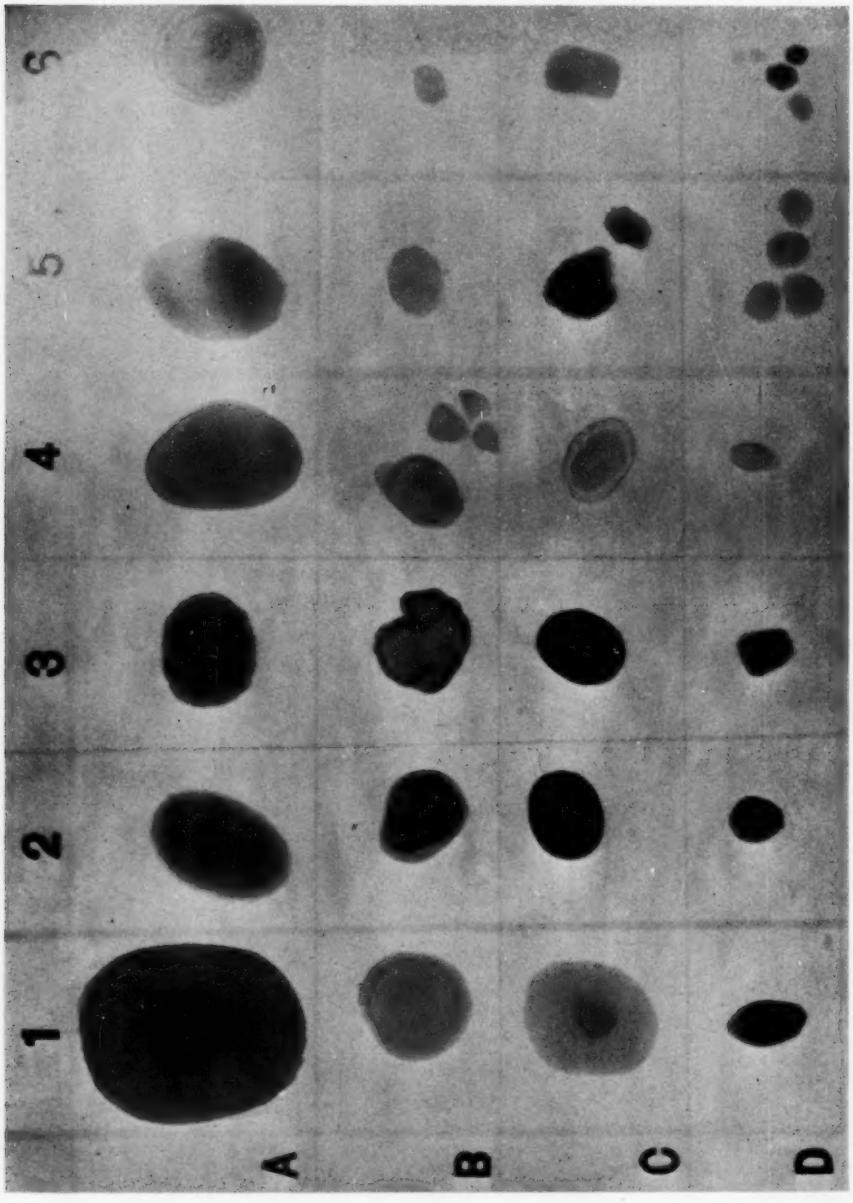

Fig. 2.—X-ray of the stones shown in Fig. 1.

Post-mortem findings of a case of keratomalacia in an infant were reported by Wilson and DuBois in 1923, with keratinization of the epithelium of the renal pelvis.[22, 23] Rats are said to develop keratiniza-

tion of the urinary epithelium after ten weeks of vitamin A privation, at the same period during which urinary infections and stones occur.[7] In other words, the mucosa is changed to skin or becomes skinlike.

The crusts which sometimes form on the skin about urinary fistulas, and preputial calculi are interesting in this connection. The question naturally arises as to whether these accretions are due to the skin surface tension alone or to the bacterial flora of the skin.

We attempted to develop a technique for the study of the morphology of the nuclei of these solitary bladder stones, searching especially for keratinized epithelium. Scrapings from the hand were mixed with pure uric acid; smears were made and studied with various stains, none of which proved satisfactory. Never could any epithelial elements be identified in the smears that were known to contain epithelium. Repeated smears from the nuclei of the stones showed nothing, except upon one occasion when three of twelve smears from different stone centers, stained at the same time with Gram's stain and decolorized with analine (two parts) and xylol (one part), showed elements which resembled epithelial cells. These may have been artefacts, but it is rather striking that they all appeared in the same staining batch. The photomicrographs were not retouched. (Figs. 3, 4, and 5).

Evaluation of a dietary with respect to vitamin A is difficult, and the conclusions may be considered conjectural.[8] Nevertheless, a study of the foods available in a typical Syrian market during a period of one year seemed to show that the diet was lacking in vitamin A content except for the green vegetables and fruits, and these were available during only part of the year.

Dairy products, which are ordinarily rich sources of vitamin A, are scarce and probably have a very low vitamin A content in Syria. The cows live on dry fodder for a considerable part of the year. Milk and cream are white, not yellow. All the milk is boiled immediately after milking and again before use. Butter is not used as such, but it is heated to high temperature to "clear" it, very much as lard is rendered. It seems probable that the milk has a small vitamin A content due to the poor diet of the cows and goats and that this small amount is destroyed by boiling the milk and by rendering the butter at high temperatures. By the use of the chemical color test for vitamin A, none could be detected in ordinary samples of native butter. Adding commercial vitamin A concentrate to boiling butter makes the color test become strongly positive, but it becomes negative again with a few minutes' boiling.

The seasons during which the fresh foods are available differ in various parts of the country, but transportation of garden stuffs has not been developed to any great extent. The existence of some seasonal dietary insufficiency might be suggested by the voracious ap-

Fig. 3.

Fig. 4.

Fig. 5.

Figs. 3, 4, and 5.—Photomicrographs of stained smears of substance from the centers of three solitary bladder stones from children. Elements which resemble epithelial cells are seen in all three.

petites of the people for green foods of all kinds. Unripe grapes, green almonds, green apricots, raw cow peas, and lettuce are eaten in large quantities as soon as available. Green leaf vegetables were available only during the winter and spring in the market we studied. The common variety of carrots in Syria is white. Of all the foods which Mendel classes as "excellent sources" of vitamin A, eggs alone were found to be plentiful during the months from April to August.

Further evidence of a lack of vitamin A might be adduced from the occurrence of sporadic cases and epidemics of night blindness,[3] and the prevalence of trachoma and corneal opacities.

The incidence of urinary calculi in the adult population does not fall within the scope of this paper. In children we found no kidney calculi and only one case of ureteral calculus.[2] The symptoms of bladder stone are so dramatic that the diagnosis is easy. The children with bladder stones had been breast fed, but the Syrian mother usually also allows the infant to try to eat any food that is available.

CONCLUSIONS

1. Solitary urinary bladder stones are not uncommon in small boys in Syria.

2. The condition is not due to obstruction of the bladder outlet.

3. Neither heredity nor the aridity of the climate nor infections seem to be prime causative factors in this group of cases.

4. Observations are presented which are consistent with the theory that the stones form about keratinized urinary epithelium caused by seasonal vitamin A privation.

The authors gratefully acknowledge the help of Dr. Harry R. Boyes, Tripoli, Syria; Dr. Ellis Herndon Hudson, formerly of Deir ez Zore, Syria; the medical faculty of the American University at Beirut, especially Professor Stanley E. Kerr; Dr. Abdul Lateef Bisar, Tripoli, Syria; Dr. Waheeb Nini, Tripoli, Syria; Dr. Herbert Torrance, Tiberias, Palestine; Dr. Ernest Wyder, Nazareth, Palestine.

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DISEASE IN THE AMERICAN NEGRO

I. Melanoma

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A NUMBER of observers noted the fact that melanoma, in either benign or malignant form, occurs in the negro race with relative rarity.[1-5] Adequate explanation for this surprising fact has not been found. It is intended here to review the facts from previously reported cases and to report ten new cases, so that the rarity and peculiarities of these tumors in the negro may be emphasized.

It is well known that certain types of neoplasms, such as fibromyomas of the uterus, have a greater incidence in the negro. The view seems to persist, however, that malignant tumors are less common in negroes. Adler and Cummings[6] noted the apparent rarity of malignancy in West African natives. Sequeira and Vint,[7] however, do not believe malignancy is rare in African natives, and quote figures from examination of surgical specimens at a native hospital. They found squamous-cell carcinoma of the skin or mucous membranes to be the most frequent type of malignancy and melanoma next. Bishop[1] noted that skin tumors appeared to be less common in the negro, but did not think that there exists any racial immunity to cancer in general. It would seem that in any discussion of racial tendencies to neoplastic growth, particular types of tumors must be compared. Few studies of this nature have been made on the American negro. Extensive investigation of this nature, compared with similar studies from Africa, might reveal additional information about the etiology and nature of cancer.

Matas[8] in 1896, having noted the relative infrequency of melanomas in negroes, suggested that in highly pigmented people the physiologic function of pigment formation was under better biologic control, and so less liable to uncontrolled growth. Morestin[9] reported a melanoma on the foot of a negro. Weiting and Hamdi,[10] in a study of 10,000 deeply pigmented oriental people and negroes in Constantinople, found only 6 melanomas, 2 of which were from the sole of the foot and from the eye. None of the 6 patients were deeply pigmented. Among 7 cases of malignant melanomas reported by Hazen,[11] 1 was in a negro and started on the bottom of the foot. Sutton and Mallia,[12] reviewing this subject in 1923, found reports of only 6 cases of malignant melanoma in the negro, and reported an additional case arising in the toe. Adler and Cummings,[6] in their study of malignancy in West African natives, mentioned 1 case of melanoma which arose from the foot. In 1927 Bauer[2] reviewed the 14 cases which had been reported up to that time and reported 2 cases, 1 arising from a toe and 1 from a thumb.

Received for publication, May 3, 1940.

Dickson and Jarman[13] reported a case of subungual melanoma. Bishop[1] reported 9 cases. Butterworth and Klauder[14] reported 1 case. Hewer[15] presented figures from the autopsy and surgical pathology laboratories of Johns Hopkins Hospital to indicate the rarity of melanoma in the negro and concluded that melanomas were more than three times as common in white people as in negroes.

Affleck,[5] in a series of 215 benign melanomas, reported only 1 in a negro. Among 317 malignant melanomas, only 2 were in negroes. Individual cases of malignant melanomas in negroes have been reported recently by Herold,[16] Moragues,[17] and Baxter.[3] Pack and Adair[4] in 1939 stated that only 34 cases of melanoma in negroes, excluding African natives, have been reported. Among their series of 477 melanomas, 7 were in negroes. The real rarity of melanomas in American negroes is thus attested by the fact that less than 50 cases have been reported. It is probable, however, that the real incidence is greater than this figure would suggest.

According to a review by Baxter,[3] 224 cases of malignant melanoma have been reported in colored races. The exact number reported from African negro races of the same origin as the American negro and the comparative incidence, is difficult to determine. Several reports indicate that in African natives melanoma may be more common. Des Ligneris[18] noted 17 cases among native patients in Northern Transvaal, all except 1 occurring on the skin of the leg or foot. Sequeira and Vint,[7] as previously noted, found melanomas next in frequency to squamous-cell carcinoma among skin tumors in African natives. Hewer[15] stated that malignant melanomas were frequent among the natives of Anglo-Egyptian Sudan. Baxter[3] concluded that melanotic tumors in the African native often remain locally malignant, less frequently metastasize, and have a slower course than melanoma in the American negro.

Baxter's figures respecting location are interesting. Among 170 cases he collected from the literature, 65.3 per cent occurred on the foot. A definite relationship to trauma appears to be borne out, though it must not be overlooked that the relatively light pigmentation of this region may have some bearing on this frequency of location.

With the exception of Affleck's[5] report, there is a striking absence in the literature of studies on the comparative incidence of benign pigmented nevi in the white and colored races. Such a study should be very instructive, although most of the malignant melanomas reported in the negro have not arisen from previously noted benign growths.

REPORT OF CASES

Ten cases of malignant melanoma from negro patients were found among 14,000 surgical specimens at the John Gaston Hospital in Memphis. No cases were observed at autopsy during a five-year period.

Twelve malignant melanomas were observed from white patients during the same period, though the proportion of white patients seen at this institution is only 22 per cent. These figures suggest that malignant melanoma is about four times as frequent (4.2:1) in the white race as in the negro.

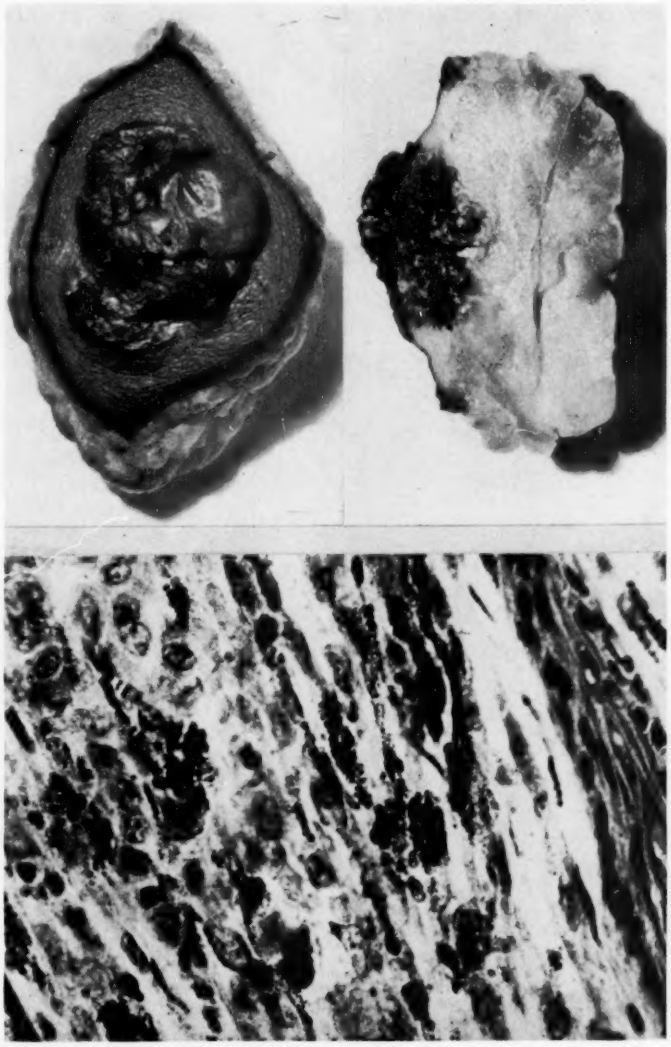

Fig. 1.—Case 1. Malignant melanoma of the right hip, as seen on the outer surface, bisected showing the cut surface, and in microscopic section. The abundant melanin pigment is evident.

CASE 1.—A negro woman, aged 26 years, had a small growth on the right hip, present since birth. Two months before admission to the hospital she bruised the tumor and subsequently scratched it. Since that time increase in size had been noted, so that it formed a firm, elevated lobulated dark tumor mass, 4.5 cm. in diameter. The adjacent regional lymph nodes were enlarged, firm, and on section showed dark pigmented areas. The tumor was a papillary type of growth, the neoplastic cells in the subepithelial portion being thin or spindle shaped, but becoming more rounded in deeper portions. In the regional nodes solid dense

masses were formed by rounded or oval cells with little tendency to be spindle-shaped. Melanin was quite abundant in the tumor and metastases. (Fig. 1.)

CASE 2.—A negro man, aged 55 years, injured his left great toe while working in a lumber yard. The nail was split and he removed it himself, but complete healing never occurred. Four years later the toe was noted to be markedly enlarged, and soon nodules developed on the leg and in the left groin.

Biopsy from the toe showed masses of large pale tumor cells in the subepithelial tissue. Melanin was very abundant. Most of the cells were round or oval, except in focal areas occupied by spindle-shaped cells, with a tendency to pattern formation.

Fig. 2.—Case 4. The primary pigmented ulcerated tumor in the popliteal region and the metastatic tumor mass in the inguinal region.

CASE 3.—A negro female, aged 37 years, developed a painless swelling of the left foot, which grew to form a mass 3 cm. in diameter. Metastasis later developed in the leg. Amputation was performed, but death occurred from intercurrent infection. At the time of amputation the tumor was seen as an ulcer measuring 5.5 cm. situated on the dorsum of the foot. The base of this ulcer was black in color, and the edges were elevated and indurated. Microscopically, most of the cells appeared to be elongated or spindle-shaped forms. Pigment was quite abundant.

CASE 4.—A negro male, aged 73 years, noted a painful nodule on the leg which increased in size and became ulcerated. Nine months later a nodule was present in the left inguinal region which progressed to ulceration, the tumor appearing as a dark grayish black tissue. Microscopically, melanin pigment appeared to be very abundant. Most of the tumor cells had an oval or polyhedral shape, and were arranged in cords or solid sheets. Mitoses were numerous. (Fig. 2.)

CASE 5.—A negro female, aged 25 years, had noticed a small thickening of the skin on the sole of the left foot for eight years. This grew steadily larger and became elevated and tender. A similar nodule appeared on the instep and other

pigmented nodules on the foot and left hip. Small nodules could be felt in the left inguinal region.

Microscopic study of the primary tumor of the foot showed marked variation in size, shape, and staining qualities of the tumor cells. The cells were predominantly polygonal in shape. Brownish black intracellular pigment was abundant.

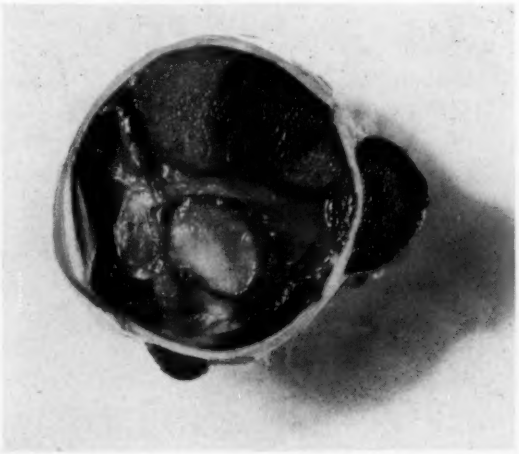

Fig. 3.—Case 8. Sectioned surface of eye, showing the highly pigmented tumor within the chambers of the eye and on the outer surface.

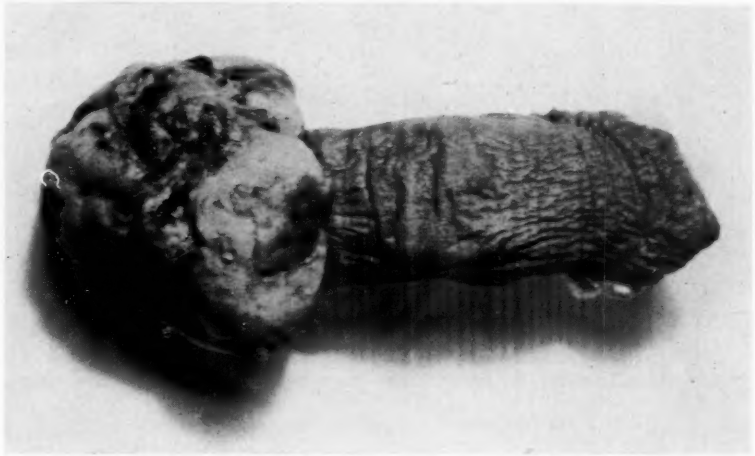

Fig. 4.—Case 9. The left ring finger, showing the large fungating tumor mass involving the end of the finger.

CASE 6.—A negro male, 40 years of age, injured his left foot from a tack in his shoe. A small abscess formed in this area, which discharged purulent material. This remained tender and never completely healed. Nine months later a tender, deeply pigmented area was noted just medial to the point of injury. About the same time a swelling was noted in the left inguinal region. The pigmented region of the foot became slightly elevated and was removed. Pigmented material was prominent in the subepithelial tissue, and irregularly infiltrating downward. The inguinal mass was composed of soft, black tissue. Microscopically, the cells were polyhedral and spindle-shaped, showing considerable variation in morphologic characteristics and numerous mitotic nuclei. Pigment was abundant.

CASE 7.—A negro woman, aged 50 years, noticed a small elevation of the skin between the third and fourth toes of the left foot. Four months later, following considerable discomfort from an ill-fitting shoe, the tumor enlarged, became painful and finally ulcerated.

The tumor appeared as a soft, fungating, and ulcerated mass separating the toes. Operative removal of the third and fourth toes, including the tumor mass, was performed. The tumor appeared to have arisen at the junction between dorsal and plantar surfaces.

Microscopically, the tumor cells varied a great deal in shape and size, but were predominantly of spindle form. Mitoses were numerous, and pigment was abundant. The superficial portion of the tumor was infected. Enlarged inguinal lymph nodes showed inflammatory changes but no metastatic tumor cells.

Fig. 5.—Case 10. Showing the very large metastatic tumor mass involving the left axilla.

CASE 8.—A negro male, aged 66 years, became blind in the left eye. Six months later he noted a small round black area, about the size of a pinhead, at the sclerocorneal junction. This gradually increased in size, so that three years later, when medical aid was sought, irregular brownish black masses of soft friable tissue were protruding through the eye.

The eye was enucleated, and the eyeball was found to be practically filled with dark brown tumor tissue, growing beneath the retina and pushing that structure forward. The individual tumor cells were elongated or spindle-shaped and contained abundant melanin pigment. The tumor cells infiltrated the sclera and in some areas had broken through and were proliferating on the external surface of the eye. (Fig. 3.)

CASE 9.—A negro male, aged 59 years, suffered a crushing injury of left ring finger. The fingernail came off, but the wound appeared to heal satisfactorily.

Six months later, following a minor injury to the same finger, a small tumor was noted on the posterior surface of the distal phalanx. This increased in size to form a rounded fungating tumor mass, 6 cm. in diameter. Microscopically, there was but little melanin pigment evident. Mitoses were numerous. The cells varied from oval to spindle shape and were highly anaplastic. (Fig. 4.)

CASE 10.—A negro male, aged 46 years, developed a small black nodular tumor growing out from under the edge of the nail of the left thumb. There was no history of trauma. The thumb was amputated. One year later a small mass was noted in the left axilla. This gradually and painlessly increased in size, forming a very large, lobulated dark brown tumor. The tumor was highly cellular and vascular, with abundant pigment. The cells were polymorphous, being round, polyhedral, and spindle-shaped. (Fig. 5.)

Comment.—In this small series of 10 cases the findings emphasized from previously reported cases have been corroborated. In 5 cases the melanoma arose from the foot and in 6 cases there was a definite history of antecedent trauma. An unusually large proportion, 30 per cent, appeared to have a subungual origin. Seventy per cent were derived from regions of the skin which normally contain relatively little pigment. In only 1 case was there a definite history of a previous benign growth at the same site. There seemed to be little significant age or sex difference in this series, though the 4 females varied from 25 to 50 years of age, and the 6 males from 40 to 73 years.

Microscopically, nothing distinctive could be found in this series of malignant melanomas. They appeared quite comparable to the malignant melanomas found in white patients. The tumors varied markedly in the amount of pigment they contained. The morphology of the tumor cells was likewise variable.

Thus, while there seems to be a definite difference in the incidence of malignant melanoma in the white and negro races, no qualitative difference in the tumors has been noted. A definite relationship to traumatic injury is frequent with malignant melanomas in the white race also, though this factor seems unusually prominent in the negro. The incidence of benign pigmented tumors in the negro race does not seem to have been investigated seriously. It is evident, of course, that benign pigmented tumors are apt to be overlooked in heavily pigmented skins unless attention is drawn to them by traumatic injury or malignant change. Consequently the impression obtained from published reports that malignant melanoma in the negro rarely arises from a pre-existing benign growth may be quite misleading. The racial difference in the occurrence of a neurectodermal tumor, the melanoma, suggests the possibility that investigations of racial incidence of other types of tumors arising from structures of the peripheral or central nervous system may reveal significant facts.

SUMMARY

1. Ten cases of malignant melanoma arising in American negroes are reported. These occurred in a series of 14,000 surgical specimens, ap-

proximately 78 per cent of which were from negroes. Twelve malignant melanomas were encountered from white patients in the same series of surgical specimens. Thus in this series the relative incidence of malignant melanoma in the white race was more than four times that in the American negro.

2. The frequency with which malignant melanoma in the negro arises in the foot and follows traumatic injury is re-emphasized.

3. No morphologic differences were noted in the malignant melanomas arising in negroes as contrasted with those in the white race.

The author is indebted for the illustrations in this study to Dr. J. L. Scianni, Artist, University of Tennessee Pathological Institute.

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CROSS-INFECTIONS FROM ANESTHETIC FACE MASKS

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INFECTION from an anesthetic face mask is a known hazard.[1] The possibility of the transmission of influenza by anesthesia apparatus has been suggested.[2] In the presence of active pulmonary tuberculosis with a positive sputum this cross-infection is a real hazard. All too frequently only a cursory washing of anesthetic masks between anesthesias is performed. Autoclaving of apparatus after each anesthesia may be practiced; however, this not only necessitates the use of sterilizing apparatus that often is carrying a capacity load of other operating room supplies, but also demands constant attention by the anesthetist to prevent overheating, with its resultant softening and deterioration of rubber parts. A face mask left in a 10 per cent solution of cresol overnight may cause a skin burn when applied with pressure for a long operation.[3]

We wish to report the results of guinea pig inoculations of saline washings of anesthetic masks removed from patients having active pulmonary tuberculosis. Specimens were taken as follows: (A) after removal of the mask from the face; (B) after washing the mask with water, as is the custom in many institutions; (C) after washing the mask as in (B) and then immersing it for one hour in the following solution:

Formaldehyde (38 per cent solution)	210 c.c.
Aqua	606 c.c.
Alcohol 95 per cent q.s. ad	4,000 c.c.

This solution was made by one of us (G. M. D.) after bacteriologic investigation to determine the lowest percentage of formalin necessary to destroy the tubercle bacilli in less than one hour.

The first specimen (A) was collected from the mask by swabbing it with a sterile swab previously moistened with saline solution. Specimens B and C were saline washings of the entire mask. Specimen A was emulsified in about 2 c.c. of sterile saline solution and injected subcutaneously in guinea pigs. Specimens B and C were individually centrifuged for one hour and the 2 c.c. of the solution in the bottom of the centrifuge flask were removed from each and injected subcutaneously in guinea pigs. These animals were necropsied at the end of eight weeks. Gross evidence of tuberculosis was present at this time; the inguinal lymph nodes were enlarged and caseous and tubercles of the liver, spleen, and other organs were present. In each animal smears were made from this caseous material and acid-fast organisms were demonstrated.

The results obtained from the bacteriologic examination of the anesthetic masks removed from patients with active pulmonary tuberculosis

Received for publication, May 11, 1940.

TABLE I

PATIENT	SPECIMEN			PATIENT	SPECIMEN		
	A	B	C		A	B	C
E. B.	+	–	–	J. B.	+	–	–
A. J.	+	–	–	J. B.	–	–	–
A. J.	–	–	–	J. B.	–	–	–
A. J.	–	–	–	J. H.	–	–	–
R. B.	+	–	–	E. N.	+	–	–
A. N.	–	–	–	R. B.	–	–	–
H. S.	–	–	–	R. B.	–	–	–
W. S.	–	–	–	L. L. (control)	+	–	–
A. M.	+	+	–	A. M. (control)	+	–	–
J. I.	–	–	–	A. M.	–	–	–
J. I.	–	–	–	A. M.	–	–	–
H. S.	–	–	–	L. L.	+	–	–
J. M.	+	+	–	B. J.	–	–	–
E. Bl.	–	–	–	M. B.	+	–	–
E. Br.	Animal died early	+	–	M. B.	–	–	–
				D. M.	–		–
D. N.	–	–	–	B. S. (control)	–	–	–
D. N.	–	–	–	B. S.	–	–	–
D. N.	–	–	–	G. (control)	+	+	–
D. N.	+	+	–	R. H.	–	+	–

appear in Table I. In the 39 anesthetic face masks examined 13, or 33.3 per cent, contained tubercle bacilli when removed from the patient's face; 6, or 15.4 per cent, still were contaminated with tubercle bacilli after being washed in water according to the technique all too frequently employed; whereas none contained tubercle bacilli after being washed in water and then soaked for one hour in the formaldehyde-alcohol solution.

DISCUSSION

Most, but not all, of the anesthetics administered were for thoracoplasty operations. All of the patients had active pulmonary tuberculosis. Some of the patients had very little sputum at the time of operation, which may account for many of the negative specimens in Column A. It apparently made no difference what stage of thoracoplasty was being performed, as some masks showed contamination on the first stage and others only on later stages. The last patient (R. H.) was known to have a Gaffky 10 sputum. Apparently this sputum was not secured in the swab Specimen A. The results marked "control" indicate the placing of sputum from patients known to have very active pulmonary tuberculosis on face masks and then making the same examinations.

As a routine it has been found practical to remove the anesthetic mask, breathing tubing, breathing bags, head straps, and other removable parts of the anesthetic apparatus from the solution at hourly intervals. After removal, all of these parts should be thoroughly washed with soap and hot water until the odor of formalin cannot be detected. This is necessary in order to avoid a skin burn during the next adminis-

tration and to eliminate the irritating formalin fumes from the apparatus. We have observed no deleterious effect to the patients or the apparatus. This procedure has been employed for seven years in a large series of cases in our institution. The formaldehyde-alcohol solution was preserved for use on several occasions.

SUMMARY

Bacteriologic examinations of 39 anesthetic masks removed from patients with active pulmonary tuberculosis revealed contamination with tubercle bacilli in 33.3 per cent of the cases. That these masks must be carefully handled to prevent spread of the disease is obvious.

Over 15 per cent of these masks still contained active tubercle bacilli after the type of washing ordinarily employed and were a potential source for the spread of tuberculosis.

No bacteriologic evidence of tubercle bacilli remained after immersing the masks for one hour in the formaldehyde-alcohol solution described in this communication.

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OBSERVATIONS ON CAPILLARY PERMEABILITY IN AREAS OF INFLAMMATION PRODUCED BY STAPHYLOCOCCI*

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IT HAS been shown recently that trypan blue following an intravenous injection in the rabbit localizes and concentrates in areas of inflammation produced by the local application of xylol only when the dye is given within a period of three hours following the application of the irritant. The skin remains hyperemic and edematous, however, for several days following the application of xylol.[1, 2]

Menkin in studying inflammation injected 0.1 c.c. of a saline suspension of *Staphylococcus aureus* into the dermis of the abdomen of rabbits and a few hours later gave the animals an intravenous injection of trypan blue. He observed that "within a relatively short time the tissues in the site of inflammation appeared markedly stained. In many cases these areas showed a pale reddish central zone surrounded by an intensely dark blue band measuring about 0.5 cm. in width. The localization of intravenously injected trypan blue in inflamed areas of the dermis was evident in thirty-two out of thirty-six experiments. The central zone which has a red congested appearance and which is often seen in these intracutaneous areas of inflammation is perhaps due to thrombosis of small vessels. Histological sections of such areas reveal some thrombosed vessels with acute inflammatory changes in the surrounding tissue."[3]

It is important to compare the localization and concentration of trypan blue in areas of inflammation produced by staphylococci with that which occurs following the application of xylol. Especial attention is given in this study to the interval between the intradermal injection of organisms and the intravenous injection of the trypan blue.

MATERIAL AND METHODS

Normal rabbits are used in this study. They are carefully shaved twenty-four hours or longer before the experiment is begun.

The staphylococci are grown on extract agar at 37.5° C. for twenty-four hours. The bacteria are washed with saline solution from the agar surface and then washed three times in large volumes of physiologic salt solution. The organisms are suspended in saline solution. The concentration is sufficient to make a cloudy suspension. Two-tenths cubic centimeter of this bacterial suspension is injected intradermally at intervals varying from twenty-five hours to immediately before 10 c.c. of

*Aided by grants from the John and Mary R. Markle Foundation and the University of Tennessee.

Received for publication, May 16, 1940.

a 0.2 per cent saline suspension of trypan blue is given intravenously into the marginal vein of the ear. Several observations are made on a single rabbit.

Macroscopic examinations are made at frequent intervals. Careful observations over a period of an hour are made following the injection of the trypan blue. The skin becomes blue when the dye localizes. The presence or absence of dye in the areas of hyperemia is recorded and also the size of the area of distribution of the dye.

The original saline suspension of staphylococci is diluted with saline solution 1/10 and 1/100. Intradermal injections of these suspensions are made into some of the rabbits in studying the effects of a variation in the number of bacteria on the quantity of dye that localizes in areas of inflammation. The organisms are heated at 60° C. in a water bath for one hour, placed in the icebox for an hour, after which time they are reheated at the same temperature for a second hour. The heat-killed organisms are usually kept in the icebox overnight before they are injected. Cultures are made on blood agar plates to determine if the bacteria are all killed.

A tuberculin syringe and a 27-gauge needle are used for all intradermal injections.

EXPERIMENTAL

Local Inflammation Produced by Staphylococci in the Skin of the Rabbit.—Two-tenths cubic centimeter of a saline suspension of washed staphylococci are injected intradermally. Observations are made on the skin at the following intervals (Table I):

TABLE I

TIME	NO. OF RABBITS	MACROSCOPIC OBSERVATIONS
0 min.	11	No change in skin
15 min.	6	No change in skin
30 min.	7	No change in skin
60 min.	9	No change in skin
1½-3 hr.	13	Small amount of hyperemia
4-25 hr.	34	Progressive increase in edema, hyperemia, and frequently focal necrosis

A histologic study on the skin of four rabbits in which the staphylococci are given intradermally at intervals varying from fifteen minutes to twenty-four hours before the animals are killed shows a progressive increase locally in the number of leucocytes. Definite abscesses are present two hours after the bacteria are injected. Some thrombosed vessels are present; however, they are infrequent.

The time in which the leucocytes first appear in the tissues where the killed bacteria are injected is approximately the same as when they appear in the areas injected with the live organisms.

Localization of Trypan Blue in Areas of Inflammation Produced by Staphylococci.—The preceding experiments show that the macroscopic

evidence of inflammation produced by the staphylococci used in this study occurs only after one hour. Polymorphonuclear leucocytes begin to infiltrate the tissues, however, after only a few minutes.

The rabbits used in the preceding experiment were injected intravenously with trypan blue. The following data (Table II) are the macroscopic observations on the localization of trypan blue in the areas of skin previously injected with the bacteria. These observations are made within fifteen minutes following the injection of the dye.

TABLE II

TIME	NO. OF RABBITS	MACROSCOPIC INFLAMMATION	LOCALIZATION OF TRYPAN BLUE
0 min.	11	None	Small amount of dye at point of entry of needle
15 min.	6	None	Small amount of dye
30 min.	7	None	Largest amount of dye localized during this period
45-60 min.	9	None	
1¼-1½ hr.	4	Hyperemia and edema	
2-3 hr.	10	Hyperemia and edema	A smaller amount of dye than observed between 30 min. and 1½ hr.
4-5 hr.	4	Skin shows hyperemia, edema, and necrosis	Only a narrow zone of dye is present around the periphery of the necrotic areas
6-8 hr.	4	Skin shows hyperemia, edema, and necrosis	
16-20 hr.	13	Skin shows hyperemia, edema, and necrosis	
21-25 hr.	13	Skin shows hyperemia, edema, and necrosis	

It is evident from the above data that trypan blue localizes in areas of skin where staphylococci have been previously injected when there is no macroscopic evidences of inflammation. Furthermore the greatest quantity of dye localizes in areas of inflammation when it is given intravenously within a period of three hours following the intradermal injection of the bacteria. When there is hyperemia, edema, and necrosis only a narrow zone of trypan blue localizes at the periphery of the necrotic area.

Four rabbits are given 0.2 c.c. of the following dilutions of staphylococci intradermally in studying the effect that a variation in number of staphylococci might have on the localization of trypan blue in areas of inflammation; the original suspension, 1/10 and 1/100 dilutions of the original suspension. The bacteria are injected intradermally at varying intervals preceding the intravenous injection of 10 c.c. of trypan blue. Fig. 1 shows the location of trypan blue in the skin in one of these rabbits after thirty minutes. It appears that the quantity of dye that localizes in areas of inflammation is only partly influenced by the number of bacteria injected. After ten minutes there is no dye in any of the areas where a 1/100 dilution of this suspension of staphylococci is given to two of these four rabbits. There is a diminution in the size of the areas of inflammation and the amount of dye where the 1/100 dilution is injected as compared with the undiluted suspension.

Observations on the Localization of Trypan Blue in Areas of Inflammation Produced by Killed Staphylococci.—The preceding experimental observations show that edema and hyperemia apparently are not the factors that determine the localization of trypan blue in areas of inflammation. A saline suspension of killed staphylococci when injected intradermally in the rabbit produces hyperemia and edema and polymorphonuclear leucocytes infiltrate the local area of the corium. To study the localization of trypan blue in areas of inflammation produced by killed staphylococci four rabbits are given intradermally killed organisms suspended in saline solution at varying intervals before 10 c.c. of trypan blue is injected intravenously. Table III illustrates the results observed in these rabbits. This chart also shows the variation in

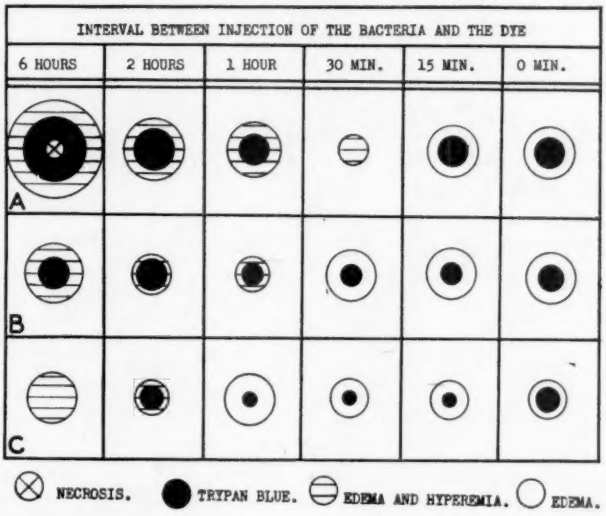


Fig. 1.—Localization of trypan blue in areas of inflammation produced by staphylococci. *A*, Suspension of staphylococci; *B*, a diluted 1/10; *C*, a diluted 1/100. Observations on necrosis, hyperemia, and edema made immediately before 10 c.c. of 0.2 per cent trypan blue was given intravenously. Location of dye recorded thirty minutes following injection.

TABLE III

LOCALIZATION OF TRYPAN BLUE FOLLOWING AN INTRAVENOUS INJECTION IN AREAS OF SKIN PREVIOUSLY INJECTED INTRADERMALLY WITH HEAT-KILLED STAPHYLOCOCCI*

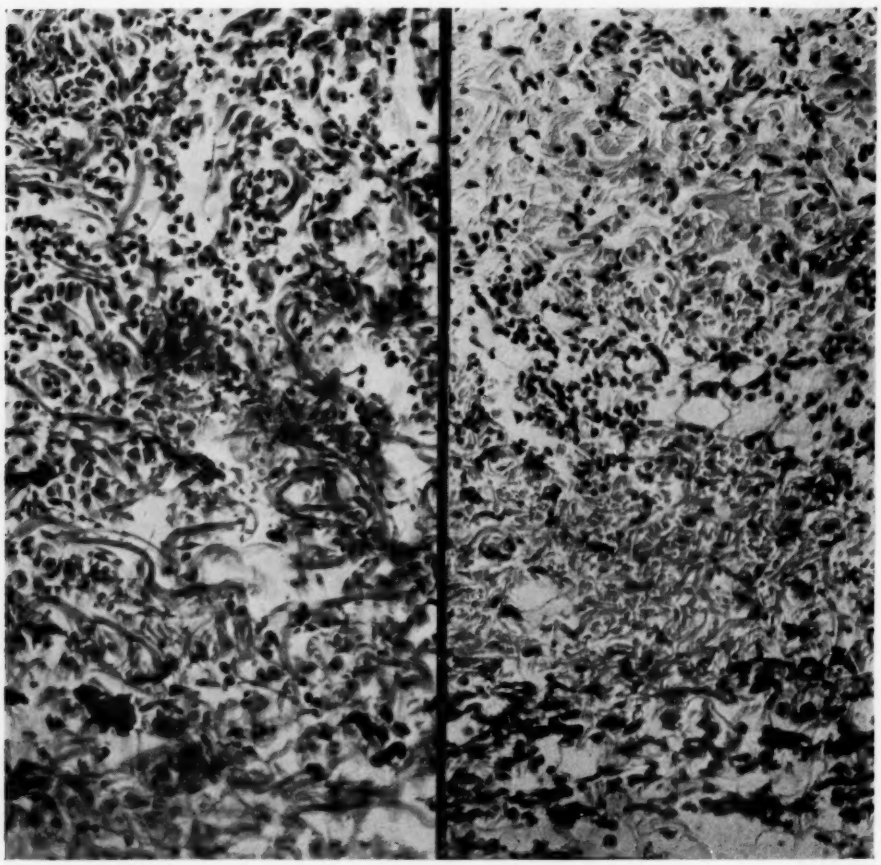
SUSPENSION† OF STAPHYLOCOCCI	INTERVAL BETWEEN INJECTION OF BACTERIA AND DYE				
	3 HR.	2 HR.	1 HR.	30 MIN.	0 MIN.
Undiluted	Hyperemia and edema	Hyperemia and edema	Hyperemia and edema	No reaction	No reaction
	No dye	No dye	Dye‡	Dye	Dye
1/10	Hyperemia and edema	Hyperemia and edema	No reaction	No reaction	No reaction
	No dye	No dye	Dye	Dye	Dye
1/100	No reaction	No reaction	No reaction	No reaction	No reaction
	No dye	No dye	Dye	Dye	Dye

*These observations were recorded thirty minutes following the intravenous injection of 10 c.c. of 0.2 per cent suspension of trypan blue.

†Milky suspension of heat-killed staphylococci in saline solution.

‡This dye was only around the point of entry of the needle and approximately an equal amount was present where each of the three dilutions of the staphylococci was injected.

the degree of reaction produced by the different dilutions of the killed organisms. Edema, hyperemia, and polymorphonuclear leucocytes may be present, but trypan blue when given intravenously fails to localize in some of the areas. There is a very small amount of trypan blue after five minutes, located about the point of entry of the needle with each of the three dilutions of bacteria injected immediately before the dye is given. Essentially the same amount of dye is present in the two



A. *B.*

Fig. 2.—*A*, 0.2 c.c. of a saline suspension of staphylococcus was injected intradermally one hour and fifteen minutes before the section was removed. Many polymorphonuclear leucocytes are present. Groups of staphylococci are present. A large amount of dye localized in this area immediately following an intravenous injection of 10 c.c. of trypan blue. *B*, 0.2 c.c. of a saline suspension of heat-killed staphylococci was injected intradermally and the section was removed after one hour and fifteen minutes. Leucocytes and groups of staphylococci are present. Very little dye localized here following an intravenous injection of trypan blue.

areas of skin injected with the undiluted suspension of bacteria thirty minutes and one hour before the dye is given. Thirty minutes following the injection of trypan blue essentially the same amount of dye is present in those areas injected with each of the three dilutions of bacteria immediately, thirty minutes, and one hour before the trypan blue is injected.

Several rabbits are injected with both live and heat-killed suspensions of staphylococci. Trypan blue localizes in certain of the areas injected with the live organisms and does not localize in the corresponding areas injected with the killed bacteria. Fig. 2 shows the local leucocytic reaction where live and heat-killed organisms are injected one hour and fifteen minutes previous to the removal of these sections. Trypan blue when given intravenously stains the areas where the live bacteria are, while essentially no dye localizes in the area where the heat-killed bacteria are located.

DISCUSSION

The observations made in this experiment show that trypan blue following an intravenous injection may localize in areas of skin previously injected with staphylococci when there is no evidence of macroscopic inflammation. The localization of trypan blue in areas of skin injected intradermally with staphylococci apparently cannot be correlated with either edema, hyperemia, or the presence of leucocytes. Similar observations were made on the localization of trypan blue in areas of inflammation produced by the local application of xylol. In the experiment with xylol the greatest quantity of dye localized in the last area where the irritant was applied immediately before the dye was given.[2]

The present experiments support the observations and opinion previously expressed on the relation of capillary permeability as shown by the localization of trypan blue to local leucocytosis.[2] It would appear that the rabbit's skin becomes blue following an intravenous injection of trypan blue as a result of a change in the permeability in the capillaries and extravascular cells. This change in the permeability may occur simultaneously with edema and hyperemia; however, it may be absent in areas of edema and hyperemia as shown by the failure of such areas to stain blue following the intravenous injection of trypan blue.

It is suggested that the staphylococcus may elaborate a substance in vivo which injures tissue cells. If the injury is mild, the cell will take up the colloidal particles of trypan blue. If the injury is severe and the cell is destroyed, it cannot take up the dye and thus the area of necrosis will not become blue. This opinion is based upon the diffuse localization of trypan blue in those areas where staphylococci are injected within a period of three hours before the dye is injected. At this time apparently the permeability of the greatest number of cells is changed, permitting the localization of the dye either in or on the cells. Edema and hyperemia may be present in other areas of the same rabbit; however, there occurs a diminution in the quantity of trypan blue that will localize when the organisms are injected several hours previously.

Thrombosed capillaries do occur in areas of inflammation as pointed out by Menkin[3]; however, an insufficient number of such vessels have been found in these experiments apparently to account for the failure of

trypan blue to reach areas of inflammation where the bacteria are injected six to twenty-four hours previously.

In any study on the localization of a dye in areas of inflammation it appears important to make frequent observations immediately following the injection of the dye in order to separate localization and concentration from retention of colloidal dyes in areas of inflammation. It has been shown that trypan blue is always retained for a longer time in those tissues that show inflammatory changes than in the normal skin.[2] It must also be remembered that the interval in which trypan blue may localize in areas of skin previously injected with staphylococci will be influenced by the virulence of the bacteria, the number of organisms, and the susceptibility of the animal.

SUMMARY

Trypan blue when given intravenously to rabbits localizes and concentrates in areas of skin previously injected with a saline suspension of staphylococci in the greatest quantity where the bacteria are injected within a period of three hours previous to the injection of the dye.

There is no relation between edema and hyperemia and the localization and concentration of trypan blue in areas of inflammation produced by staphylococci.

Essentially no dye localizes in areas of the rabbit's skin previously injected with killed staphylococci, although corresponding areas injected with live organisms in the same rabbit will become blue following an intravenous injection of trypan blue.

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Editorial

The Sphincter of Oddi

RECENT anatomical and physiological studies have revealed anew the complexity of that sheath of intrinsic muscle fibers which encloses the common bile duct in its short course through the wall of the duodenum. Improved maceration techniques[1] indicate that, in addition to newly described "reinforcing fibers" which strengthen the corners of the window through which the duct enters the duodenum and "connecting fibers" which tie the duct to the margins of the window and help erect the papilla, there are three sphincter bands which are present in varying degree in different individuals. Of these, the *sphincter choledochus*, a well-developed sheath of muscle fibers encircling the bile duct from its entrance into the duodenum to its junction with the pancreatic duct, is the one muscle (in the varying patterns of termination of these ducts) that is always so placed as to obstruct the flow of bile and to cause it to back up into the gall bladder during intervals between meals.

The second ring, the *sphincter pancreaticus*, encloses the end of the pancreatic duct just before it joins the bile duct in about one-third of all individuals. The part it plays in regulating the flow of pancreatic juice is not yet apparent, but it is of interest to note that in the chimpanzee the duodenal portion of the accessory pancreatic duct is always enclosed by a strong sphincter.[2]

The third ring, the *sphincter ampullae*, is well developed in only one-sixth of all individuals. Curiously enough, this is approximately the percentage of patients in whom reflux of contrast media into the pancreatic duct has been demonstrated by cholangiography,[3, 4] the implication being that in this percentage of the population spastic contraction of the muscle around the ampulla of Vater creates a common passage through which the contents of one duct may pass into the other. More recently the reflux of pancreatic juice into the biliary tract has been demonstrated in man[5] and has been proved to be an agency for the production of pigment stones in an experimental animal.[6]

Physiologically, there now exist experiments upon cholecystectomized and choledochostomized patients which have tested simultaneously the pressure and rate of flow in the common bile duct and the pressure in the duodenum following sudden distention of the common duct. These have demonstrated not only that the human sphincter of Oddi can act independently of the duodenal musculature, but that the intense pain induced by suddenly distending the common bile duct can be correlated only with spasm of the sphincter.[7, 8]

Treatment for spasm of the sphincter in biliary disease has resulted in much experimentation. To date temporary relief has been obtained principally from such drugs as amyl nitrite[9] and the slower working nitroglycerin.[9, 10] Thus, Bergh has recently demonstrated in 144 experiments upon cholecystectomized and choledochostomized patients[11] that out of twenty-four drugs tested only these two consistently relaxed the biliary outlet. Atropine, epinephrine, and pilocarpine were so ineffective or variable as to suggest that the regulation of the sphincter mechanism through the autonomic nervous system is relatively unimportant. However, the spasm-producing action of morphine and opium compounds[9] was fully confirmed.

Especially significant were the findings with respect to the ingestion of egg yolk in 12 additional patients. In the absence of the gall bladder, the mean reaction in these 12 patients was as follows: At the beginning of the experiments the average initial sphincter resistance was 17 cm. of water. After an average delay of 4 minutes the resistance of the sphincter decreased an average of 7 cm. over a period averaging 19 minutes, then gradually rose over a period of 15 minutes (10 cases) to the original level. These observations seem to be closely correlated with the well-known facts regarding the first phase of emptying of the human gall bladder.[12] It was even noted that in one-half the cases resistance at the sphincter increased during the 4-minute period before relaxation set in, thus confirming the writer's earlier deduction that the frequently occurring "2-minute pause" in the initial phase of emptying of the human gall bladder is due to an initial increase in tone of the sphincter. Comparison of data in these two studies thus would seem to leave little doubt that contraction of the gall bladder and relaxation of the choledochoduodenal junction after ingestion of a fatty meal are independent reactions to the same stimulus and do not necessarily involve a reciprocal relationship between the two regions.

Judging from the ineffectiveness of the reaction of the sphincter to the adrenergic and cholinergic drugs[11] and the failure of experimentally induced spasms of the stomach to prevent emptying of the human[13] (as contrasted with the animal[14]) gall bladder, one would be justified in assuming that the human sphincter is not significantly under control of the autonomic nervous system.

Nevertheless, section of the descending nerves on the posterior aspect of the hepatic artery recently has been undertaken as a means of permanently relieving spasm of the human sphincter.[15]

In a report of the first case Reich states that severance of this nerve in a patient receiving choledochostomy was followed by a lowering of intraductal pressure from approximately 12.5 to 8.5 cm. of saline solution. Assuming that the sphincter had been eliminated by this act, he concludes that the residual pressure must be due to the tonus of the duodenal muscle. While we are awaiting confirmation of this experiment, it may be noted that special methods of staining and dissecting

this plexus in cats have revealed the existence of a separate nerve to the choledochoduodenal junction (named by us the gastroduodenal nerve[16]), but that this is distributed to both the sphincter of Oddi and the adjacent duodenal muscle. Current studies now being made on the human newborn suggest that an even more complex arrangement exists in man. It is not believed, therefore, that severance of this descending plexus would result in loss of tone of just one set of muscles. Moreover, it would not be expected that severance of a nerve to smooth muscle would abolish the reaction of that muscle to morphine, although Reich infers that failure of the intraductal pressure to be maintained in this patient, after morphine was due to the severance of the nerve to the sphincter.

In conclusion, it should be pointed out that two problems, among others, await special attention: one, the means of alleviating biliary stasis in pregnancy, the cause of which may now be attributed to a spastic sphincter of Oddi,[17] and the solution of which may well lie within the field of endocrine experimentation; and two, the need for correlating function with structure in those individuals in whom biliary disturbances have been demonstrated prior to death. Maceration studies of sphincters obtained from such sources should provide critical information, for instance, as to whether reflux of pancreatic juice into the biliary tract is to be expected in that percentage of the population which has a well-developed sphincter ampullae.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT ADVANCES IN THE STUDY AND MANAGEMENT OF TRAUMATIC SHOCK

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(Continued from the February issue.)

V. SHOCK IN VARIOUS CONDITIONS

The following summary shows the similarity between the shock that occurs in many medical and surgical conditions. The list of conditions is not complete and it is to be remembered that similarity and likeness are not to be confused. In all, or almost all, of these conditions shock is due to more than one factor, and it is only by analyzing the proper proportions in each case that a complete understanding can be gained.

Traumatic Shock.—Shock due to trauma is one of the most common forms of shock, especially in this day of the automobile and the Axis. The importance of local blood and fluid loss in experimental traumatic shock has already been pointed out. Wilson and Roome (1933) presented a dramatic clinical case confirming this experimental work, and four years later Harkins and Roome (1937) presented a study of ten cases demonstrating the same point. These latter authors found that concealed hemorrhage and extravasation of plasma into the tissues are usually greater when measured quantitatively than casual inspection of the resultant swelling would lead one to believe. Mahoney (1938) performed additional trauma to the extremity experiments with resultant decreases in the blood pressure, blood volume (and especially in the erythron), total circulating protein, and in hemoconcentration.

Hemorrhagic Shock. Shock Due to Whole Blood Loss.—This is an important factor in many types and examples of shock. The article of Lehman and Amole (1938) emphasizes the function of the spleen in the retardation of shock from hemorrhage. Recently recovered splenectomized dogs did not stand repeated withdrawals of blood as well as normal dogs.

Intra-Abdominal Apoplexy.—This type of shock due to spontaneous rupture of an abdominal visceral artery is discussed by Thompson and Dunphy (1935) and by Crile and Newell (1940). Bartlett and Bartlett (1933) also reported on shock due to intraperitoneal hemorrhage.

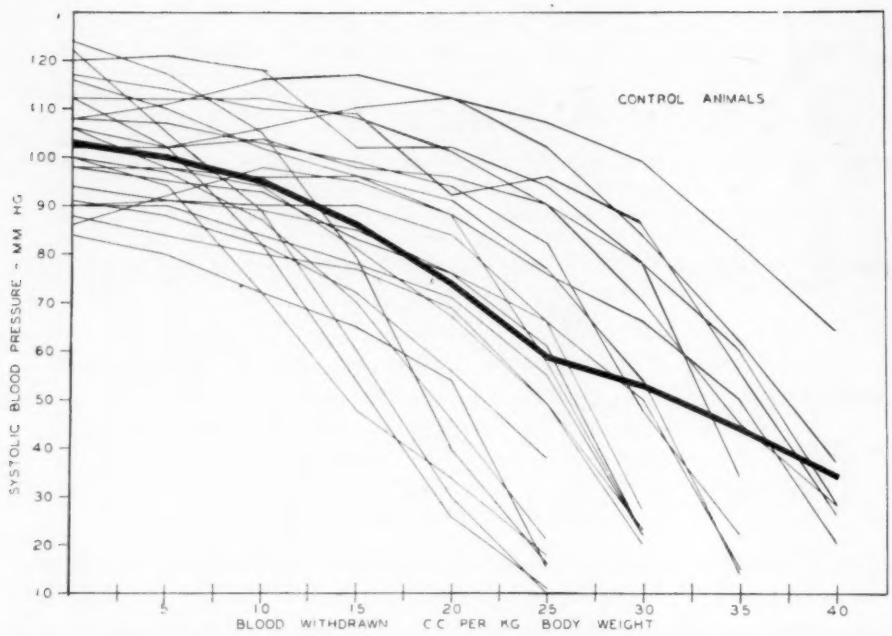


Fig. 4.—Blood pressure fall following hemorrhage in control dogs. The fine lines represent individual and the heavy line the average arterial blood pressure curves during withdrawal of 5 c.c. of blood per kilogram of body weight at five-minute intervals. (From Lehman, E. P., and Amole, C. V.: SURGERY 4: 47, 1938.)

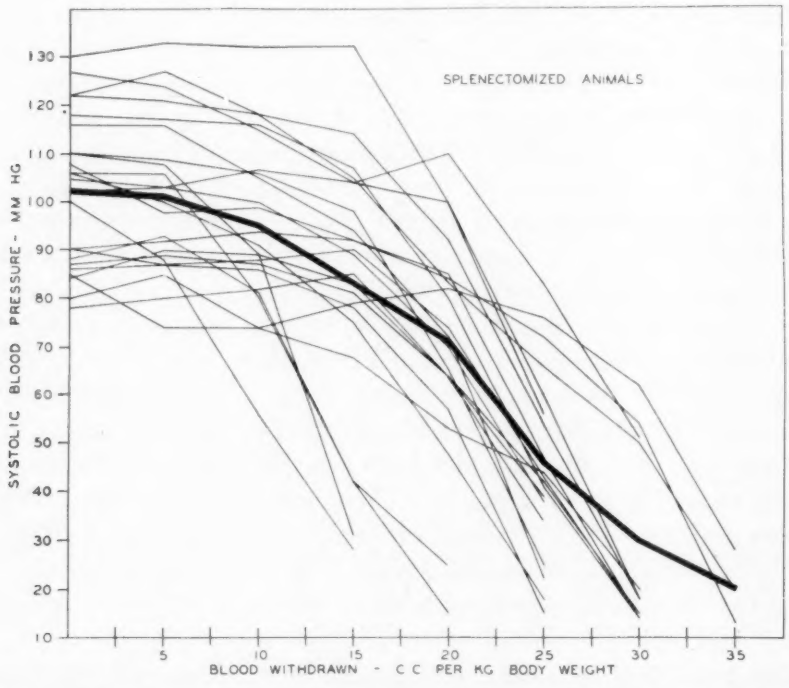


Fig. 5.—Blood pressure fall following hemorrhage in splenectomized dogs. Individual and average arterial blood pressure tracings during withdrawal of 5 c.c. of blood per kilogram of body weight at five-minute intervals. (From Lehman, E. P., and Amole, C. V.: SURGERY 4: 47, 1938.)

Shock During Operations. Operative Shock.—The important observation of Livingstone, McFetridge, and Brunner (1933) that during anesthesia "blood pressure changes, rather than an increase in pulse rate frequently present the earliest evidence of circulatory failure," should be remembered by every anesthetist. It should also be noted that, while the pulse rate is often misleading, the blood pressure often is as well. Gatch and Little (1924) determined the blood loss during surgical operations by testing the sheets, sponges, etc., and found it greater than was anticipated (mastectomy, 710 c.c.; nephrectomy, 816 c.c.; laminectomy, 672 c.c., etc.). They advised large (3 liters if indicated) transfusions to counteract this direct blood loss.

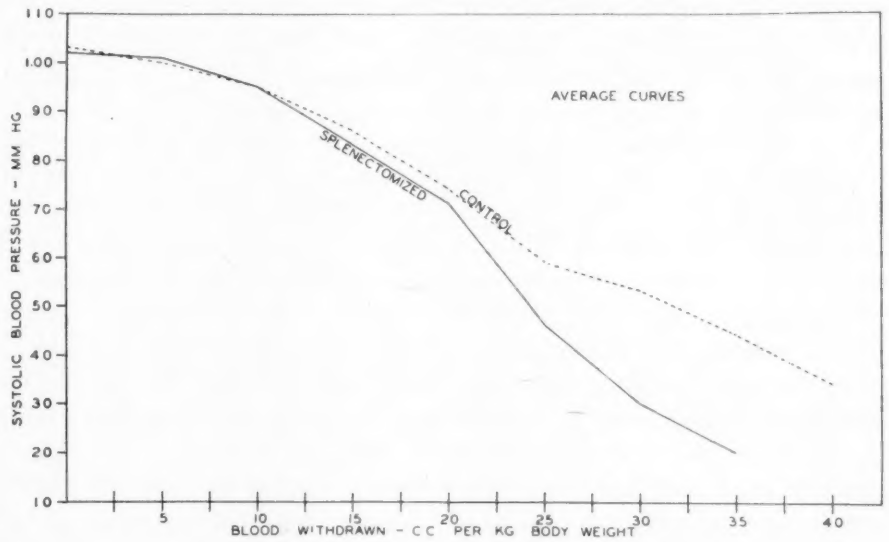


Fig. 6.—Comparison of blood pressure curves in control and splenectomized dogs following hemorrhage. (From Lehman, E. P., and Amole, C. V.: SURGERY 4: 48, 1938.)

TABLE VIII

CONDITIONS IN WHICH OLIGEMIC SHOCK MAY OCCUR

1. Hemorrhage—to outside, into tissues, into body cavities
2. Mechanical trauma—operative, accidental, trauma to intestines
3. Thermal trauma—burns, freezing, peritoneal cooling
4. Asphyxial trauma—mesenteric vascular occlusion, intestinal strangulation, tourniquet, heat stroke
5. Actinic trauma—radiation burns, sunburn
6. Chemical trauma—bile peritonitis, perforated peptic ulcer, acute pancreatitis (?), war gas poisoning
7. Trauma due to specific or nonspecific poisons—mercuric chloride, arsenicals, gold chloride, snake venom
8. Special capillary poisons—tissue autolysis, histamine, anaphylaxis, peptone
9. Medical conditions—diabetic coma, eclampsia
10. Infections—cholera, pneumonia (especially influenzal and streptococcal), gas gangrene, diphtheria, peritonitis
11. Hyperventilation
12. Spinal anesthesia

Coller and Maddock (1932) confirmed Gatch's observations and concluded: "In general, the operator is surprised to find the blood loss as high as calculated, since he does not think of the gauze sponge as absorbing much blood. . . . It is probable that most surgeons underestimate the amount of blood lost, especially in operations . . . in which wide areas of the body are uncovered with many small points of hemorrhage, control of which is attempted by gauze packing." One patient upon whom radical mastectomy was performed under nitrous oxide-oxygen anesthesia lost 1,272 c.c. of blood.

Relation of General Anesthesia and Shock.—Stewart and Rourke (1938) made studies similar to those of Mann and his co-workers, only on the effects of operation and ether anesthesia in man. They reported a lowering of plasma volume, often greater than the measured blood loss at operation would explain. Adolph, Gerbasi, and Lepore (1934) believed that amytal caused the spleen to discharge its red cells. Adolph and Gerbasi (1933) found that intraperitoneal sodium amytal administration in dogs led to a blood dilution. The results of Elman, Weiner, and Cole (1935) are not entirely compatible with this, for they found that the usual dilution of blood occurring in dogs after a single large hemorrhage under local anesthesia is absent when a similar hemorrhage is performed after the induction of intravenous sodium amytal anesthesia. There may even be concentration of the blood in the latter case. Seeley, Essex, and Mann (1936) found that the exudation from experimentally traumatized intestines is much less under amytal than under ether anesthesia. Amytal caused an immediate blood dilution and definitely delayed the eventual hemoconcentration and onset of shock. The series of animals experimented upon under ether, on the other hand, developed immediate and rapid hemoconcentration. Essex, Seeley, Higgins, and Mann (1936) found that ether anesthesia in the dog causes a marked increase in the erythrocyte count and the value for the hemoglobin and the hematocrit value, while sodium amytal causes the spleen to dilate markedly, which removes a considerable percentage of erythrocytes from the circulation. These results agreed with those of Searles and Essex (1936), who showed that ether anesthesia produces a hemoconcentration while amytal anesthesia results in a hemodilution.

Murphy (1940), in discussing the question of anesthesia in shock, pointed out the possible hazards of morphine. Kabat (1940) emphasized that general anesthesia (ether) increases the susceptibility of cats to shock. This may be due to the attendant decrease in muscle tone with poor venous return, to the decreased ability to adjust to changes in blood pH, and possibly to the exaggeration of depressor reflex activity. Kabat believes that spinal anesthesia may exert a beneficial effect, but puts forward no evidence to support this conclusion in his article.

A recent discussion in the *Lancet* (1940-1941) on the question of whether local or general anesthesia is best in shock is of interest. Clarke and Kessel (1940) advised local anesthesia, whereupon an editorial (Dec. 21), Hewer (1940), and Macintosh attacked this view, while Dodd (1941) and Henry (1941) supported it. The results of Pickering, Steinmeyer, and Luckhardt (1938) on the hemodynamic effects of procaine are apropos to this discussion.

Spinal Anesthesia.—The comprehensive monograph by Schuberth (1936) on the circulation in spinal anesthesia indicated from both experimental and clinical observations that the low blood pressure accompanying spinal anesthesia is a type of secondary shock. This author showed by detailed studies that there was a moderate decrease in the oxygen consumption, a slight decrease in the oxygen content of arterial blood, and a considerable decrease in the oxygen content of the venous blood and in the cardiac output per minute. However, the absence of blood concentration and of a decrease in the blood volume differentiated spinal anesthesia shock from other types of true secondary shock. Goldfarb, Provisor, and Koster (1939) have also studied circulation during spinal anesthesia.

Shock Due to Plasma Loss.—As discussed elsewhere, the loss of plasma is no less dangerous than that of whole blood, even though the red color that is associated with danger is absent from the lost fluid. "White" hemorrhage may be even more menacing than red. Harkins and Harmon (1937) reviewed the literature and collected data on the occurrence of plasma loss in ten conditions. They concluded that:

"(1) Plasma-like fluid is lost from the blood stream in a variety of conditions. These include burns, freezing, bile peritonitis, tissue autolysis in vivo, acute pancreatitis, pneumonia and pulmonary edema, intestinal manipulation, portal and mesenteric obstruction, externally strangulated colostomy loops, and release of a constrictor of an extremity.

"(2) The types of trauma which produce these conditions can be roughly divided into (1) thermal trauma, (2) chemical and bacterial trauma, (3) mild continued mechanical trauma, and (4) capillary injury due to inadequate circulation.

"(3) The amount of plasma-like fluid lost in these conditions approaches that which, when removed experimentally in plasmapheresis experiments, will produce death. Even in cases where the amount of fluid lost is not sufficient to cause death, it is often of sufficient importance to be recognized."

The data upon which these conclusions were based are summarized in Tables IX to XII. Many of the following conditions in which shock occurs are accompanied by an extensive plasma loss.

TABLE IX

A COMPARISON OF THE CONCENTRATION OF CERTAIN SUBSTANCES IN BLOOD PLASMA AND IN THE FLUID LOST FROM THE BLOOD STREAM IN VARIOUS CONDITIONS*

FLUID	SUGAR	NaCl MG. PER 100 C.C.	NONPROTEIN NITROGEN	PROTEIN GM. PER 100 C.C.
1. Burns	134	686	66	7.6
2. Freezing	67	697	50	3.6
3. Bile peritonitis	60	516	32	4.3
4. Tissue autolysis in vivo	83	565	71	7.6
5. Acute pancreatitis	No data	No data	No data	No data
6. Pneumonia and pulmonary edema	No data	631	No data	No data
7. Intestinal manipulation	221	616	61	6.2
8. Mesenteric obstruction	215	577	36	3.0
9. Externally strangulated colostomy loops	137	689	21	4.5
10. Release of a constrictor of an extremity	No data	619	47	4.4
Average	131	622	48	5.2

*Control values for blood plasma were: sugar, 104; NaCl, 676; nonprotein nitrogen, 54 mg. per 100 c.c.; protein, 4.2 Gm. per 100 c.c.

TABLE X

BLEEDING VOLUME IN VARIOUS CONDITIONS IN WHICH PLASMA HEMORRHAGE OCCURS*

CONDITION	BLEEDING VOLUME PER CENT BODY WEIGHT
1. Burns	1.6
2. Freezing	2.0
3. Bile peritonitis	1.8
4. Tissue autolysis in vivo	2.2
5. Acute pancreatitis	No data
6. Pneumonia and pulmonary edema	No data
7. Intestinal manipulation	1.4
8. Mesenteric obstruction	No data
9. Externally strangulated colostomy loops	No data
10. Release of a constrictor of an extremity	No data
Average	1.8

*Control values for the bleeding volume of animals under barbital have been reported: 5.2, 4.5, and 4.17 per cent of body weight. In primary types of shock the bleeding volume is usually above 3 per cent (e.g., following histamine injections, 3.6 per cent), and in secondary types of shock is below 3 per cent (e.g., following trauma to an extremity, 1.7 per cent).

Burns.—The literature on this subject has recently been reviewed by Harkins (1938), so only a brief mention of a few reports will be made at this time. Harkins, Wilson, and Stewart (1935) found no evidence of toxic action in protein-free extracts of burned skin. Harkins (1934-1938) in a series of eight papers studied burns especially from the standpoint of fluid loss and shock. This work was essentially an extension of that of Blalock (1931) and its chief contribution was the obtaining of a time curve of the edema at the site of the burn by means of a tipping apparatus connected with a kymographic tracing. The one side of an anesthetized animal which was burned gradually

TABLE XI

BLOOD CONCENTRATION IN VARIOUS CONDITIONS IN WHICH PLASMA HEMORRHAGE OCCURS

CONDITION	HEMOGLOBIN: INCREASE AS PER CENT INCREASE OVER CONTROL READING	HEMATOCRIT: INCREASE AS PER CENT INCREASE OVER CONTROL READING
1. Burns	27	28
2. Freezing	40	40
3. Bile peritonitis	48	43
4. Tissue autolysis in vivo	37	42
5. Acute pancreatitis	No data	No data
6. Pneumonia and pulmonary edema	66	No data
7. Intestinal manipulation	48	No data
8. Mesenteric obstruction	57	No data
9. Externally strangulated colostomy loops	No change	No change
10. Release of a constrictor of an extremity	No data	No data
Average	46	38

TABLE XII

TOTAL PLASMALIKE FLUID RECOVERED IN VARIOUS FATAL CONDITIONS EXPRESSED AS PERCENTAGE OF BODY WEIGHT*

CONDITION	LOSS OF PLASMALIKE FLUID IN PER CENT BODY WEIGHT
1. Burns	3.2, 2.2
2. Freezing	2.6
3. Bile peritonitis	2.5
4. Liver autolysis peritonitis	2.6
5. Acute pancreatitis	No data
6. Pneumonia and pulmonary edema	No data
7. Intestinal manipulation	No data
8. Mesenteric obstruction	5.2
9. Externally strangulated colostomy loops	No data
10. Release of a constrictor of an extremity	3.5
Average	3.1

*Control values in death following plasmapheresis have been reported as 2.6 per cent body weight (Johnson and Blalock, 1931), 4 per cent (Harkins and Harmon, 1937) and 4.4 per cent (Roome, Keith, and Phemister, 1933).

became heavier than the unburned side and the curve of this increase in weight gave a quantitative record of the increase in local edema. In previous experiments Blalock burned one side of thoroughly anesthetized animals and found at death that the weight of the two sides after bisection indicated an excess in weight of the burned side averaging 3.34 per cent of the body weight. More recent observations on burns include the following: Wilson, Rowley, and Gray (1936) and Wilson and Stewart (1940) found adrenal cortical extract of help in the treatment of burns. Trusler and associates (1939) used transfusions in burn treatment. Gunther (1939) stated that stasis in small vessels is an important factor in shock due to burns. Elkinton (1939) has added new evidence to the theory that fluid loss is of importance in burns. Greenwald (1940) discussed the overactivity of the adrenals

in the early stage. The paper of Keeley, Gibson, and Pijoan (1939), demonstrating the decreased blood and plasma volume in burns, is of importance. It not only confirms the results of previous workers but makes the conclusions more accurate, the new dye (Evans blue) method being used in these determinations. It is to be remembered that late deaths following burns are not due to shock in many instances any more than are late deaths after operation. Blalock (1934) realized that what causes death at an early period in a disease is not necessarily the fatal factor all through it. With regard to burns, still retaining his ideas as to the importance of fluid loss in the early hours, he stated: "I believe that deaths which occur from three to ten days following severe burns are due in large part to the absorption of protein decomposition products."

Freezing.—Harkins and his associates (1934-1937) found that the changes accompanying experimental local freezing are quite comparable to those resulting from its thermal relative, burning. Thus, hemoconcentration, lowered bleeding volume, decreased blood pressure, and decreased blood flow occurred. However, these observations are of little practical interest since local freezing of this extent rarely occurs, the patient usually succumbing to the general effects of the cold before shock can intervene.

Roentgen Irradiation Shock.—Moon, Kornblum, and Morgan (1940, 1941) reported a shocklike condition accompanied by hemoconcentration following experimental roentgen radiation of the abdomen.

Influenza.—Underhill and Ringer (1920) showed that lung edema in this condition acted much as did war gas poisoning. Erythrocyte counts to 9,000,000 and hemoglobin values to 140 per cent were noted. Even in ordinary lobar pneumonia the local loss of fluid may be of importance, even if it is not the chief factor. This has been emphasized by Moon (1938). Andrews and Harkins (1937) studied the lungs and pleural fluid in twenty-three pneumonia patients. The increase in weight averaged 2.81 per cent body weight, and these authors concluded that under certain conditions this loss may be significant and, if rapid enough, may result in a shocklike condition.

War Gas Poisoning.—The pioneer work of Underhill (1918, 1919, 1920) has established the importance in this condition of local fluid loss into the lungs with resultant hemoconcentration and shock. Wilson and Goldschmidt (1919) and others have extended this work.

Peptone Shock.—The classic experiments of Simmonds (1917, 1918) showed that peptone shock and fat embolism shock differed in many important respects; in fact the effects of the latter were accomplished primarily through respiratory embarrassment. Dragstedt, Eyer, and Ramirez de Arellano (1938) showed that vitamin C does not protect against peptone shock in dogs, and Eyer, Dragstedt, and Ramirez de

Arellano (1938) also showed it to be without beneficial preventive effect in anaphylactic shock in dogs. Peptone shock in fetal dogs has recently been studied by Dragstedt, Ramirez de Arellano, and Lawton (1940).

Constriction of an Extremity (Tourniquet).—The paper of Wilson and Roome (1936) is of great practical value. These authors emphasized that the use of the tourniquet may be dangerous from the standpoint not only of the local gangrene but also of general shock. They showed that release of a constrictor that had been in place too long will give such a marked loss of fluid into the tissues that this cause alone will produce shock. Allen (1939) has shown that this action of the tourniquet in producing capillary damage may be prevented in part by keeping the extremity very cold while the constrictor is in place. The studies of Allen (1939) on the production of experimental shock by release of a constrictor to an extremity are of interest. This author not only has produced shock by this means but also has found that whole blood or plasma is of benefit in its treatment.

No review of recent work on shock would be complete without reviewing the recent work of Allen (1937-1939) on the temperature factor in the use of the tourniquet. This author repeated and confirmed the conclusions of Wilson and Roome (1936). He showed that there are two factors in the causation of secondary shock on release of a tourniquet: (1) the length of time of ligation and (2) the amount and nature of the tissue ligated. In man fatal shock is known to result from constriction of the thigh for an uncertain time. Blocking of the circulation of the upper arm has also caused fatal shock upon release after a very long time. This is the smallest mass of peripheral tissue known to produce fatal shock by ligation and later release. Reasoning from analogy with experimental animals, Allen (1938) concluded that a tourniquet below the elbow could not give rise to fatal shock regardless of the time before release.

Allen did a large number of tourniquet experiments on rats, developing a standardized technique whereby in a large series of animals the relation of time of constriction to development of local necrosis or generalized shock could be plotted. This not only gave interesting information in itself, but furnished a standard method for future quantitative shock experiments. At room temperature the leg tissues were found to withstand a constriction of over fifteen hours. The most interesting point about Allen's work, however, is that as the temperature was progressively raised the effects of asphyxia were accelerated as regards production of both local gangrene and systemic shock. Contrariwise, when the temperature was reduced, these effects were retarded. Near 0° C. recovery was possible after ligation for fifty-four hours. Furthermore, when a poison, such as strychnine, was introduced into a limb, a suitable series of treatments with tourniquet and refrigeration allowed the animal to tolerate many times the fatal dose without harm. These experiments

have important implications not only for the subject of shock, but also for a myriad of other surgical problems including local infection, gangrene, amputation, etc.

Allen concluded: "A temperature slightly above 0 degrees C. in a limb reduces the metabolism of the tissues so as to enable them to withstand absence of circulation for hours or even days. . . . It is believed that this principle has definite applications in practical limb surgery."

Intestinal Strangulation.—Studies indicate that in all types of intestinal obstruction shock is liable to result from fluid loss. In strangulation obstruction this is particularly due to local loss of plasma and blood. The paper of Scott and Wangensteen (1932) is one of the earliest reports of the importance of local fluid and blood loss in experimental intestinal strangulations and their relationship to the degree of shock present. Elman and Cole (1932 and 1934) found a similar important local fluid loss in acute portal obstruction. Aird (1935) demonstrated the importance of blood loss in strangulation obstruction. Aird and Henderson (1937) showed that there is a moderate amount of histamine in the peritoneal transudate from strangulated intestinal loops. Knight and Slome (1936) studied the amount of fluid loss in strangulation obstruction and ascribed to it an important but only accessory role. In a later paper (1937) Knight attributed a toxic role to depressor substances contained in the peritoneal exudate. Later work of Maycock (1938) indicated that these products were toxic, but not markedly lethal, and hence of little importance in the picture of strangulation obstruction. The article of Scott (1938) dealing with experimental strangulation obstruction emphasizes the role of blood and plasma loss in such cases. Scott found little evidence for either direct or transperitoneal absorption of "toxic products," except terminally. He concluded: "Whole blood and plasma are apparently lost from the general circulation in quantities sufficient in themselves to account for the symptoms of shock and death which occur in most cases of strangulation obstruction" and "when venous occlusion predominates the loss of whole blood is the chief factor, and when arterial occlusion predominates the loss of plasma is important." The anemia found by Scott following venous obstruction differs from the observations of Harkins (1937) on venous mesenteric thrombosis in human beings where marked hemoconcentration was likely to occur. Fine, Fuchs, and Gendel (1940) reported that in dogs decompression of the distended small intestine retards or prevents the progressive and eventually fatal loss of plasma that they found to result from distention. Fine, Hurwitz, and Mark (1940) also found a marked plasma loss in acute intestinal obstruction.

Mesenteric Vascular Occlusion.—Mesenteric vascular occlusion may be divided into four chief clinical types: (1) portal vein thrombosis, (2) mesenteric vein thrombosis, (3) mesenteric artery occlusion usually

embolic in origin, and (4) intestinal strangulation in which both veins and arteries are occluded. Experimental workers have shown that obstruction of these vessels is accompanied by an effusion of blood and bloody fluid into the peritoneal cavity, into the tissues supplied by the vessels in question, and into the lumen of the involved gut. This effusion has been found large enough, in many instances, to account for death of the animals on the basis of secondary surgical shock. Few clinical reports of the relation of such bloody effusion to resultant shock and death were found in the literature. The reports of Harkins (1936, 1937) on a study of nine cases indicate that such an effusion may be important clinically. An analysis of these cases showed that in most instances there was a plasmalike effusion into the peritoneal cavity with concomitant hemorrhagic infarction of the involved bowel. However, the blood and blood pressure studies and analyses of the peritoneal fluid in the early cases were inadequate to determine the amount of plasma and blood loss. After the study was begun, one case of fatal venous thrombosis with infarction of 240 cm. of intestine was more carefully investigated. There was extensive loss of several liters of bloody fluid into the involved bowel, peritoneal cavity, and from the stomach by vomiting with marked blood pressure fall and hemoconcentration (hemoglobin 143, hematocrit 61). The peritoneal exudate was chemically similar to blood plasma. A study of these cases indicated that effusion of circulating blood fluids may be a factor in the production of surgical shock and resultant death in patients as well as in laboratory animals. Boyce and McFetridge (1935) studied the importance of shock in mesenteric vascular occlusion and Boyce, Lambert, and McFetridge (1935) investigated it in experimental occlusion of the portal vein. The importance of local blood loss in these two related conditions was stressed. Aird (1938), using the vital red method of determining blood volume, noted a marked decrease in experimental strangulation where the veins were occluded.

Peritonitis.—The importance of shock in this condition has been pointed out by Moon (1938) and others. Harmon and Harkins (1934, 1937) made a study of the vasodepressant substances present in the peritoneal fluid. In 1935 they found no reduction in the bleeding volume in the shock state that accompanies acute experimental colon bacillus intoxication, and hence classified the condition as primary shock. In all types of peritonitis local fluid loss is of importance, but especially is this true of bile peritonitis as shown in the following section.

Bile peritonitis.—Mason and Lemon (1931, 1932) pointed out that dehydration might be an important factor in death from liver autolysis. Previous ideas concerning death in this condition and in bile peritonitis had centered around the toxic and the anaerobic bacterial theories. In a series of five papers Harkins, Harmon, Andrews, and Hudson (1935,

1936 and 1937) studied the exudate in experimental bile peritonitis and found it to be plasmalike in composition. This indicated the possibility that not merely a dehydration, but an actual shocklike condition might be a lethal factor. This was borne out by the finding of the exudate in appreciable amounts (2.2 per cent body weight) with associated blood pressure fall, hemoconcentration, and decrease in the bleeding volume. While the shock due to local fluid loss was not considered to be the entire explanation of death, it was considered to be important. In liver autolysis peritonitis the role of anaerobic bacteria seemed to be more important. These findings concerning bile peritonitis have since been verified by Manson and Eginton (1938). These latter authors also concluded that "secondary shock from loss of fluid from the vascular system" is of importance. Unfortunately, this work has not as much practical value as would appear, because human bile is much more dilute and hardly irritating enough to duplicate the shock syndrome found by Harkins and his co-workers in dogs. Hence, this experimental work cannot be applied to patients without reservations. Blalock (1935) found gastric juice less irritating to the peritoneal surfaces than bile. Using dog bile or bile salts, Andrews, Harkins, Harmon, and Hudson (1937) found that a similar shock syndrome to bile peritonitis was produced by the subcutaneous injection of bile. There was local plasma exudation and general hemoconcentration, etc. Davis (1940) found that shock resulted from subcutaneous hypertonic (25 per cent) saline injections much the same as that following Harkins, Harmon, and Hudson's subcutaneous bile injections. However, while the bile produced an outflow of plasmalike fluid, the salt produced a much more aqueous edema.

Peritoneal Irrigations.—These have already been considered in the experimental portion of this paper. Doménech-Alsina (1932) produced shock with hemoconcentration and oligemia by means of peritoneal irrigations of hypertonic solutions. Perla and Sandberg (1939) showed that intraperitoneal glucose produces a rise in serum potassium.

Peritoneal Cooling.—Mahoney (1938) induced shock by placing often renewed cold saline packs between the folds of the mesentery of anesthetized dogs for a period of one to one and one-half hours. A decrease in blood pressure, blood volume, and especially plasma volume, and total circulating albumin occurred. Only a slight blood concentration resulted and the author presented no definite evidence to explain the site of the lost plasma.

Trauma to the Intestines.—Blalock (1931) was the first to demonstrate the true importance of local fluid loss in this condition. In a series of twelve dogs the average loss was 4.48 per cent of the body weight. Red cells constituted only a small part of the fluid that escaped from the peritoneum covering the intestines. Storck and Ochsner (1936) also noted a fall in blood pressure following experimental intestinal

stripping. Swingle and Parkins (1935) did not agree with previous workers that shock could be produced by intestinal stripping. They found that "even two and one-half hours of vigorous stripping of the entire length of the small intestine between the fingers does not induce shock, nor significant lowering of the arterial pressure." Schachter and Huntington (1940) found that dogs given oral desiccated thyroid went into shock much more easily following intestinal manipulation than normal dogs.

VI. THERAPY OF SHOCK

This most important aspect of the subject has been much clarified within the past few years. The rationale of empirically proved remedies has been studied, and a trend away from symptomatic treatment has been noted. For purposes of simplification, treatment will be divided under four heads: (1) standard or empirical treatment, (2) fluids, (3) oxygen, and (4) adrenal cortical extract.

1. Standard Treatment.—This includes remedies arrived at empirically, some of which are logical, while others should be discarded.

a. *Rest and Quiet.*—As with many treatments, this has a different rationale according to what theory one ascribes. Thus, it will prevent nociceptive stimuli; it will prevent squeezing toxins out of injured parts; or it will prevent continued bleeding and local fluid loss. No matter what the theory, rest and quiet are advisable.

b. *Elevation of Feet.*—In all cases of shock or impending shock this seems to be advisable, precaution being taken that respiration is not interfered with. Selby (1940) advised inversion of the patient as a first-aid measure in shock. In the hospital the foot of the bed should be raised and in the open the plan can be applied most simply by the stretcher bearer at the foot carrying the handles of the stretcher on his shoulders, while the rear stretcher bearer suspends the head end at full arm's length. Howat (1940) and Seldon (1940) also advised elevation of the feet as an emergency measure in counteracting shock.

c. *Warmth.*—The importance of cold in the initiation of shock was shown by the Shock Committee during World War I, by Blalock (1934), and Harkins and Harmon (1937). Warmth, then, certainly seems advisable, but too generalized heat of too high a degree might precipitate a too sudden capillary dilatation. In Cologne, at the University Surgical Clinic, Hilgenfeldt, the assistant of von Haberer, advises against too great heat for this reason in burn shock. The new electrically heated cage ("Restor" shock cage) recently described in the *Lancet*[670a] is of interest.

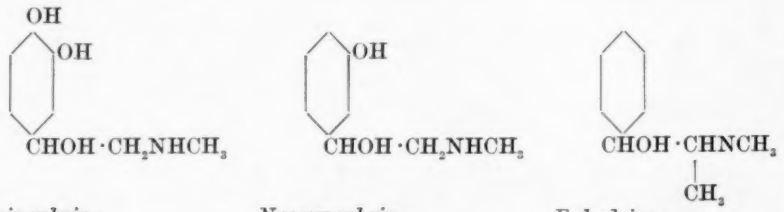
d. *Sedatives.*—These were advised by those who propagated the nervous theory, but as long ago as 1922 Cannon warned against too free a use of morphine in shock. Morphine is apt to exaggerate any anoxia that is present. The recent paper of Blalock and Cressman (1939) has

exploded the idea that spinal anesthesia is of benefit in shock. The type of general anesthesia to be used also depends on the cause of shock. Because ether was said to be harmful in histamine poisoning, adherents of the histamine theory advised nitrous oxide-oxygen anesthesia. In the presence of anoxia this latter would seem to be a poor choice.

e. *Stimulants.*—The use of stimulants would seem to be mainly symptomatic and contradictory to the use of sedatives. It is possible, however, that caffeine might be helpful in anoxia.

f. *Vasopastics.*—A perusal of the work on production of shock by adrenalin alone, discussed in a previous section, would certainly make one hesitant in using that drug in the treatment of shock. Especially is this true when it is realized that there is already a vasoconstriction present. The use of adrenalin, as advised by Guthrie (1917) and others and opposed by Atchley (1935) and others, arose because of the false concept that the peripheral arteries were relaxed in shock. In the blood pressure fall accompanying spinal anesthesia this is true, but not in real "secondary shock." Hence the use of adrenalin should be abandoned in true shock.

Despite the experimental evidence against use of the vasospastics in shock, they will be tried empirically until the objections are more definite. Johnson in 1930 advised the use of ephedrine sulfate and in 1937 suggested the use of neosynephrin hydrochloride in the treatment of acute shock from trauma and hemorrhage. So far no experimental evidence has been brought forth against the use of this latter compound. Its structural formula closely resembles that of epinephrine and ephedrine as shown by the following:



Epinephrine *Neosynephrin* *Ephedrine*

A usual dose of 5 mg. of the drug was given subcutaneously to six patients in shock, five of whom recovered. In several cases the dosage was repeated. Although the results in this series were good, the type of patient varied considerably, and adjuvant treatment with blood transfusions was used in two cases. It therefore seems that a larger series should be studied before the drug can be advised routinely. Wood (1939), of Melbourne, also used neosynephrin with good results. He advised it in conjunction with an intravenous drip of large amounts of glucose saline solution and blood transfusions.

Even some writers who heartily advocate the use of neosynephrin hydrochloride in maintaining blood pressure during spinal anesthesia

recognize that this does not mean it is applicable to secondary shock. Thus, Silvers and Leonard (1940) state that "neosynephrin . . . is not effective in cases where there is loss of blood volume or shock caused by toxic conditions such as peritonitis."

In Germany where the treatment of shock is still symptomatic in many clinics, two tyramine derivatives, veritol and sympatol, are used extensively. Sympatol is obtained from tyramine by the addition of a methyl and hydroxyl group, while veritol is obtained by adding two methyls. Thus, these two compounds are quite similar to adrenalin in their action. Reports on the action of veritol in shock were made by Büssemaker (1938), Herkel (1938), Parade (1938), Cobet (1938), Baron (1938) and Kalk (1938). Colombi, of Milan, favors veritol plus normal saline solution in shock therapy. Devine (1939), of Melbourne, has also used veritol in shock. In a small series of cases only two out of ten consecutive patients failed to respond to its administration with a rise of blood pressure of over 20 mm. of mercury.

Kunkel, Stead, and Weiss (1939) found that paredrinol (α-N-Dimethyl-p-Hydroxyphenethylamine) may be of aid in some types of blood pressure fall, but that in the type of shock resulting primarily from loss of fluid from the blood stream the drug is of little value and may even be harmful.

Dodd (1940) has recently reviewed the effects of various drugs used in surgery to raise blood pressure. His remarks can be summarized as follows:

1. *Coramine:* "No effect whatever is produced on the blood pressure, nor has any other benefit been observed."

2. *Adrenaline:* "Adrenaline is regarded as useless for the purpose of raising and maintaining the blood pressure in surgery."

3. *Icoral:* "Too powerful for surgical purposes."

4. *Eserine:* "Found to vary."

5. *Ephedrine:* "Duration of the raised level is uncertain. . . . remained the chief remedy until something better was found."

6. *Cortin:* "Effect was inconsistent."

7. *Veritol* (β-*p*-oxyphenyl isopropylmethylamine): "Of the drugs so far tried it is the most satisfactory for raising the blood pressure." This drug can be given intravenously, intramuscularly, or both. Intramuscular dose is 0.75 to 1.0 c.c., rise begins in 3 to 5 minutes, maximum in about 20 minutes, duration 20 to 40 minutes, after which it should be repeated. Intravenous dose is 0.25 c.c.; rise is instantaneous and duration is 20 to 25 minutes. Combined technique of 0.75 c.c. deep into shoulder muscles and 0.25 c.c. intravenously gives immediate and maintained pressure rise for 30 to 45 minutes.

8. *Cardiazol and Veritol:* "An effective twin injection."

9. *Hypertonic Saline:* Useful in bringing up low blood pressure due to spinal anesthesia.

In a recent editorial in the *Lancet* (**2**: 813, 1940) data are reviewed which indicate that veritol (*β-p*-oxyphenyl isopropylmethylamine, an isomer of ephedrine) has no markedly superior action over other and older sympatheticomimetic drugs. In this editorial the statement is made that "experience has shown that physicians of the Continent tend to be unduly optimistic about the value of new drugs."

Freeman, Freedman, and Miller (1940) tested the effects of prolonged adrenalin injections in normal dogs without anesthesia. They used practically the same dose per minute as Gregersen and Pinkston (1936) and Hamlin and Gregersen (1939), who found no marked change in plasma volume. Freeman and associates, however, continued their injections for at least one hour to one and one-half hours and to this they attribute their finding of a definite decrease in plasma volume and a state of shock (Gregersen and co-workers continued their injections beyond 30 minutes in only a few cases). Post-mortem studies suggested that the fluid lost from the circulating blood in shock is distributed through the tissue spaces and that some of it passes through the intestinal mucosa into the lumen of the digestive tract.

2. Blood Substitutes.—This part of the treatment is in reality the sine qua non of modern shock therapy. It is not a symptomatic treatment; it attempts to get at the underlying pathology and replace what is actually lost. Four avenues of administration are available: oral, rectal, subcutaneous, and intravenous. Of these only the latter is sure enough to permit a patient's life to depend upon it. Because of difficulty in getting in the collapsed veins in shock, physicians should not hesitate to cut down on veins in case of necessity.

Oral Fluids.—The interesting experiments of van Liere, Northrup, and Vaughan (1940) indicated that oral administration of fluids during the acute phase of recovery from severe hemorrhage is not of material assistance to the organism as far as immediate restoration of blood pressure is concerned. Amounts of saline solution placed in the intestines of dogs did not restore blood pressure even though they were absorbed, while the same amounts of fluid given intravenously brought about distinct improvement. Orojejunal feeding has recently been used by Ravdin, Stengel, and Prushankin (1940) as a means of controlling hypoproteinemia in surgical patients. The importance of hypoproteinemia in the production of nephrotic edema was demonstrated experimentally by Leiter (1928, 1931). In the first publication he stated what is now common knowledge, that "edema usually begins when the plasma proteins have fallen to 3 per cent or less."

These methods, however, essentially involve maintaining nutrition of surgical patients and, important as they are in themselves, are not directly applicable to the emergency treatment of shock cases. There,

the intravenous administration of fluids is the best method. The new cellophane intravenous set developed by Hartman (1940) may solve some of the problems of administration of fluids and prevention of the reactions therefrom. The technique of fluid administration was presented by Gallie and Harris (1930).

Intramuscular Fluids.—The intramuscular injection of fluids has been used by Billimoria and Dunlop (1940) in the Department of Surgery at the British Postgraduate Medical School. The needle is inserted in the lateral surface of the thigh and usually normal saline solution or 5 per cent glucose in amounts up to 5 liters in one day is given. In more than twelve years' experience no instance of infection has occurred.

Proctoclysis.—This method is too uncertain and too slow for use in serious shock cases. Furthermore, Perusse (1932) has shown that, while proctoclysis is useful for water administration, crystalloids are not well absorbed, the use of 1 per cent glucose (thus definitely hypotonic) being the best substance to give in this manner.

Temperature of Injected Solutions.—The popular idea that intravenous solutions should be warmed to body temperature probably originated from data observed before the importance of pyrogens was discovered (1923). More recently, De Gowin, Hardin, and Swanson (1940) have concluded that with blood, at least, it is safer not to prewarm, and that any parenteral fluids are just as safe at room temperature as when prewarmed.

Intra-Arterial Injections.—Davis (1937) reported good results in the treatment of experimental shock with the intra-arterial injection of hypertonic solutions. The intra-arterial injection of 5 to 10 c.c. of a hypertonic solution resulted in an elevation of the systolic blood pressure from 10 to 50 mm. Hg, this pressor response lasting from one to three hours. The arteries used were the femoral or brachial. Twenty-five per cent gum acacia was the most effective solution; whereas, 30 per cent gum acacia was one of the least effective. Control injections of isotonic sodium chloride did not increase the blood pressure. Intravenous injections produced no pressor response nor did intra-arterial injections following spinal cord section. In fact, in shocked animals the depressor response to the intravenous injection of hypertonic solutions was quite striking and might have proved dangerous. Bilateral adrenalectomy did not completely abolish the response. The response was believed to be nervous in origin. At first it was thought that removal of fluid from traumatized areas might be responsible for the pressor rise, but later it was shown that this was too slight to be a major factor. Davis concluded that: "Intra-arterial administration of hypertonic solutions is of value, inasmuch as the elevation of blood pressure is accompanied by a more adequate blood flow to the vasomotor and respiratory centers as

evidenced by the disappearance of Traube-Hering waves and dyspneic respirations.'' At this time Davis suggested this method for possible clinical trial, cautioning that his own experimental work was still in progress. Kendrick and Wakim (1939) corroborated the findings of Davis and his co-workers on the immediate beneficial effects of intra-arterial hypertonic saline injection. The permanent effects were harmful, however, and ''death appeared to be hastened rather than delayed by the injections.'' Kendrick (1939) found that with 5 per cent glucose even the temporary benefits were greater after intravenous administration.

Intravenous Amino Acids.—Although these may be of little value in the treatment of shock, they may be of marked prophylactic value in hypoproteinemic cases, according to Elman and Weiner (1939). As Elman (1940) has shown, an average-sized blood transfusion contains only about 17 Gm. of plasma proteins and thus even several transfusions can hardly maintain protein balance, let alone restore a deficiency. Elman reported excellent results in most of a series of twenty-five patients treated with hydrolyzed casein which contains all of the eleven essential amino acids. Jejunal feeding has also been used to restore the plasma proteins. In another paper (1940) Elman pointed out that, since the serum globulin concentration and relative red cell volume both decreased following experimental intravenous injection of enzymic hydrolysate of casein, they were led to infer that the increase in serum albumin concentration was due to a regeneration.

Recent Experimental Work.—The work of Stanbury, Warweg, and Amberson (1936) on total plasmapheresis is of great interest. They found that the blood plasma could be almost totally removed from the blood vessels of cats and dogs, without injury to the animals, if the normal blood is replaced by a solution of 6 per cent gum acacia in Ringer-Locke solution in which are suspended washed red cells of the same species (30 to 40 per cent). This substitution was accomplished by alternate bleeding from and injection into the carotid artery. The plasma proteins could thus be reduced to the very low level of 0.05 to 0.15 per cent. No signs of shock or of capillary dilatation or edema appeared after such ''total'' plasmapheresis. The blood pressure was maintained and some animals recovered and lived for indefinite periods. These authors concluded that the plasma proteins have only a physical function. Further studies of total plasmapheresis in dogs were made by Etteldorf, Mitchell, and Amberson (1937).

These observations are hardly more interesting than those of Amberson and his associates Flexner, Steggerda, Mulder, Tendler, Pankratz, Laug, Webster, and Engel (1934). These authors replaced blood with hemoglobin-Ringer solution and, while the animals did not survive permanently, they lived twenty-four to thirty-six hours. Such animals,

even though they can move around, seem dazed mentally and will neither eat nor drink. Death seems to result because the kidneys are permeable to the solution and it eventually is excreted. But that these animals can exist at all with no signs of shock with a red count of about 100,000 is indeed remarkable.

The authors conclude: "The experiments throw light upon the significance of the mammalian red corpuscles. These are important (1) in maintaining hemoglobin in the reduced state, electrochemically speaking, and (2) in holding it within membranes impermeable to it so that it cannot leave the blood stream."

Other experiments indicated an almost normal oxygen consumption of these practically "erythrocyte-free" animals. All of these results are summarized in Amberson's extensive review of blood substitutes (1937). His observations are of great theoretical interest, but, in addition, have valuable implications concerning shock and its treatment.

The fluids that are available for intravenous use are included in the following list:

a. Water
b. Crystalloids, saline crystalloids (normal salt solution, Ringer's solution, Locke's solution), glucose
c. Acacia
d. Ascitic fluid
e. Whole blood (also red cell concentrate and hemoglobin-Ringer solution)
f. Plasma

With the exception that the use of ascitic fluid is still in the experimental stage, these six types of fluid are listed in approximate reverse order of preference. In discussing the relative inefficiency of crystalloids in the treatment of shock due to hemorrhage, Buttle, Kekwick, and Schweitzer (1940) concluded that plasma is the only effective blood substitute, at least so far as their experiments on cats were concerned. The other substitute solutions they placed in the following descending order of value: serum, hemoglobin-Ringer, gum-saline, red cells in crystalloid solution, isotonic saline, isotonic glucose.

a. *Water.*—The prevention of dehydration in surgical patients is important in preventing shock. The important studies of Coller and Maddock and their associates are of prime importance in this regard. Not only are these studies of interest from the prognostic standpoint, but they have led to a more adequate conception of the fate of crystalloid solutions in the body. In this regard papers include those of Miller and Poindexter (1932); Marriott and Kekwick (1937); Coller, Bartlett, Bingham, Maddock, and Pedersen (1938); Bartlett, Bingham, and Pedersen (1938); Winslow (1938); Bartlett (1939); Fuge and Hogg (1938); Nelson (1939); Elkinton, Gilmour, and Wolff (1939); Drew,

Scudder, and Papps (1940); King (1940); Emhardt (1940); Lands, Cutting, and Larson (1940); and Maddock and Coller (1940). Walter (1940) discussed the proper preparation of parenteral fluids so as to eliminate pyrogens.

The importance of dehydration as a factor in secondary shock was stressed by MacFee and Baldridge (1934), who presented data on infusions of saline solution and the effect on shock. Fuge and Hogg (1938) have also studied the question of postoperative fluid balance. They found that in a series of twelve surgical patients the average insensible fluid loss per day was 1,460 Gm. with extremes of 1,150 and 1,830 Gm. per day. The insensible loss for all cases averaged 39 per cent of the total output. It seemed to vary more with the size of the patient than with the type or extent of the operative procedure. Latimer (1939) has recently summarized the work of others on water balance and added a practical working scheme of his own. The importance of such a plan in the pre- and postoperative period will go far in the prophylaxis against shock. Recent reviews of the subject also include those of Mason and Hellbaum (1938) and Darrow (1940).

The work of Cutting and Koppanyi (1938) and of Cutting, Larson, and Lands (1939) is of interest in showing how large amounts of fluid can be tolerated by normal animals. Using cats they found that the following doses were tolerated:

Normal saline	5.1 c.c. per minute per kilogram
	706 c.c. total per kilogram
	≡ 350 c.c. per minute or 50 L. total in 2½ hr. for average-sized man
5 per cent glucose	4.2 c.c. per minute per kilogram
	465 c.c. total per kilogram

Swingle, Parkins, Taylor, and Hays (1937) showed that considerably less than this amount of fluid, when given in the form of distilled water, would lead to death in dogs.

b. *Crystalloids, Salt Solution, and Glucose Solution.*—The reports of Hoitink (1935, 1938), of Utrecht, Holland, are almost solitary in favoring crystalloid solutions over blood transfusion. He found in his experiments that none of the infusion liquids gave better results than 0.9 per cent sodium chloride solution. He concluded that after an acute dangerous hemorrhage its use is "preferable to the use of other artificial blood substitutes and to blood transfusion."

A careful perusal of Hoitink's papers reveals the following important fact. He does not state how rapidly the blood was withdrawn, except to say that it was taken from the carotid artery by means of a large cannula, and he makes no mention of the removal being intermittent. So it may be assumed that he was dealing with a *rapid* hemorrhage. The

quantity of the hemorrhage was large, averaging 5.6 per cent body weight. As to the interval before injection of the blood substitute, his only remark is that it is done "shortly afterward." Thus, this author was dealing with cases of hemorrhage pure and simple which may have been so sudden that there was no time for the irreversible vascular wall changes of shock to occur. In such a case even the advocates of the generalized capillary permeability theory of shock would not expect such an increased permeability. With the normal saline solution to preserve the blood volume and pressure, such animals should remain alive almost as well as patients with marked chronic anemia. Experiments such as Hoitink's may be, therefore, an example of the danger of applying ideas obtained from hemorrhage experiments to shock treatment. Hemorrhage that has been allowed to remain untreated so long that shock is present is, of course, a different matter. Simultaneously with Hoitink's report, Konrich (1935) arrived at exactly the opposite conclusion on the same material, finding that sodium chloride solution is inferior to all others. Neuwelt, Necheles, and Levinson (1940) also found experimentally that whole blood or plasma was markedly superior to saline solution in treating shock.

Despite these objections, salt solution has some place in shock treatment when one remembers its limitations. Lamb (1910) advised intravenous saline solution with the head of the patient lowered. Pilcher and Sollmann (1914) had early shown that saline infusions give an increased tone to the vasomotor center, both before and after hemorrhage. Cutter (1936) presented data on the effects of large volume intravenous injections, and Cutting, Lands, and Larson (1938) studied massive saline infusions experimentally. The dangers of giving isotonic crystalloid solutions too rapidly have been worked out in considerable detail by Gilligan, Altschule, and Volk (1938) and by Gilligan, Altschule, and Linenthal (1938). Scudder (1940) believes that saline solution has another virtue: The contained sodium relaxes the smooth muscle of the constricted arteriosles. The relaxing effect of salt on constricted vessels was first shown by Roy (1884).

Hypertonic Solutions: These have long been advised because it was thought that their viscosity more nearly resembled plasma and because of their osmotic action. Both of these virtues are apt to be evils at the same time and in dehydration hypertonic solutions may increase the blood volume at the expense of the all-important cell water. Murphy, Correll, and Grill (1941) in studying the effects of intravenous solutions in patients with and without cardiovascular defects observed dangerous reactions after the use of 50 per cent glucose solution.

Glucose: Except as a nutriment and protection for the liver, glucose seems to have little advantage over salt solutions in shock treatment. The value of intravenous glucose injections in shock was shown by Erlanger and Woodyatt (1917).

Danger of Excess Use of Crystalloid Solutions: This aspect of the treatment of shock has received considerable attention of late, but the series of six articles published by Blalock and his associates in 1932 and 1933 remains the most complete exposition of the subject. Beard and Blalock (1932) studied the composition of the blood during continuous trauma to the intestines when no fluid was injected and when fluid was injected continuously. They found a great decrease in the absolute value of total plasma protein in circulation following injection of normal salt or glucose solution, while blood did not give this effect. Blalock, Beard, and Thuss (1932) obtained similar results in dogs in which the blood pressure was low for unexplained reasons. They even found, when whole blood or serum was injected, if deductions were made for the protein present, in that injected whole blood or serum a great decrease in the absolute amount of plasma protein was found. The findings of Beard, Wilson, Weinstein, and Blalock (1932) and of Blalock and Beard (1932) on saline injections in experiments on trauma, graded hemorrhages, histamine injection, and spinal anesthesia were essentially the same.

Beard, Wilson, and Blalock (1933) found that, in the presence of low blood pressure produced by histamine or graded hemorrhage, subcutaneous or intraperitoneal normal saline solution would produce a decrease in the absolute amount of plasma protein. On the other hand, similar saline solution introduced by stomach tube produced no such effect. Blalock, Wilson, Weinstein, and Beard (1933) found that the introduction of pituitary solution or epinephrine did not prevent the loss of protein from the circulation in cases where normal saline solution was administered intravenously.

These ideas were extended by other writers. Horsley (1934) noted that normal salt solution escapes readily from the vessels in shock. Davis (1936, 1937) also showed that crystalloid solutions may be harmful in certain cases of shock.

In this regard it is interesting that Krogh stated (1922) in his well-known monograph on the *Anatomy and Physiology of Capillaries:* "Injections of isotonic and hypertonic solutions of various crystalloids have been exhaustively tried, but found to be useless, and it is easy to see that in cases where the permeability of the capillary wall is increased, such solutions must leave the circulation very rapidly."

Hepler and Simonds (1938) performed other experiments indicating the rapid loss of crystalloid solutions injected during shock. Shock was produced by impounding the blood in the liver and intestinal tract by means of temporary hepatic vein ligation. Injection of normal saline solution in quantities up to somewhat more than the estimated initial blood volume induced a rise in systemic pressure during the injection, but the pressure fell almost to the previous low level within from one to three minutes after the injection was stopped. They concluded: "The

rate of fall in blood pressure and reduction in blood volume after injection of salt solution under the conditions of these experiments indicates the rapidity with which fluid escapes from the circulating blood." At another point they stated "the use of such fluids is definitely contraindicated in shock." In their dogs, which received a large injection of saline solution, a surprising amount of fluid was found to have escaped into the lumen of the stomach and into the gastric submucosa.

c. Acacia.—Good, Mugrage, and Weiskittel (1934) stated: "Acacia is the dried gummy exudate of the stems and branches of Acacia Senegal or of some of the other species of Acacia. It is an inert polysaccharide of high molecular weight having an acid nucleus. It is related to the dextrins, glycogen, starch and cellulose. Like the latter it is amorphous, odorless, translucent, and on hydrolysis yields one or more sugars, generally pentoses and hexoses." The viscosity of a 6 per cent solution is much the same as plasma. The solution is somewhat acid. Analysis shows 0.5 per cent total nitrogen, which may explain some of the anaphylactoid reactions observed.

Use of colloid solutions intravenously was first made by Czerny (1894), who infused protein and acacia solutions into experimental animals. Hogan (1915) made the first clinical use of these substances, injecting 2.5 per cent gelatin solution. Gum acacia was first used clinically by Hurwitz (1917), who, stimulated by Hogan's (1915) earlier use of gelatin-saline solution, successfully treated the first cases in San Francisco in 1916. Soon, largely because of the interest of Bayliss, gum acacia was used extensively at the Western Front. The Base Hygiene Laboratory of the B.E.F. at Boulogne was soon producing 75 liters of sterile gum solutions daily (Telfer, 1919). Lack of experience with proper preparation caused some failures. For a discussion of the early development of this solution the reader is referred to the almost incomparable review by Amberson of blood substitutes (1937).

Following its use in World War I, acacia enjoyed wide popularity, especially in Great Britain and at the Mayo Clinic. White and Erlanger (1920) used it experimentally. Hancock (1938) favored it. Tui, Schrift, and Ruggiero (1939) showed that most of the toxic reactions of acacia may be due to contained pyrogen. The use of acacia in war has been recently reviewed in correspondence (1939) in the *Journal of the American Medical Association.*

Maytum (1932) reported that in a series of approximately 3,000 intravenous injections of acacia solution given at the Mayo Clinic, only one anaphylactoid reaction occurred. This was in the only patient in whom multiple injections were separated by a long enough interval to develop hypersensitiveness. In experiments on nineteen sensitized guinea pigs, seven developed severe anaphylaxis with two deaths. It was concluded that acacia is a mild antigen, and that under rare circumstances a patient may exhibit anaphylactic symptoms when a previous dose has been ad-

ministered some weeks or months before. It seems from this work of Maytum's that acacia should never be given longer than a week after the last previous and possibly sensitizing dose.

Good and Mugrage (1934) analyzed the results of administration of acacia to 111 patients in three private hospitals, 53 per cent of these patients being surgical. Most of the others suffered traumatic injuries or shock after ruptured ectopic pregnancy, etc. The dosage of acacia varied from 100 to 1,700 c.c. and 77 patients survived, a mortality rate of 30.6 per cent. Twenty-four of the patients who recovered and 6 of those who died received blood transfusions in addition to the acacia. Acacia alone raised the systolic blood pressure an average of 35.5 mm. Hg. The minimum rise was 12 mm. and the maximum rise 70 mm. Hg. In most cases the pulse rate after the injection of the gum acacia solution was lowered 10 to 20 beats per minute. In 4 instances the rate was lowered 40 to 55 beats per minute; in 8 there was no change. There were no true anaphylactic reactions, although minor disturbances, including vomiting, headache, or chills, occurred in 11.7 per cent of the cases. None of the deaths in the entire series could be attributed directly to either the gum acacia or blood transfusions.

Good and Mugrage concluded: "A colloidal solution like 6 per cent gum acacia solution is preferred to any of the crystalloidal solutions for raising and maintaining the low blood pressure of surgical shock. It is safe, ready, and inexpensive."

A very adverse report on the use of acacia comes from the University of Iowa, where Dick, Warweg, and Andersch (1935) found bad results attending its use in cases of nephrosis. While these conclusions may not be entirely applicable to other conditions, the extensive acacia deposits found in the liver and also in the bone marrow, lymph nodes, lungs, kidneys, and spleen would tend to make one cautious in using large amounts of acacia. Furthermore, once acacia has been given, blood counts and blood typing become difficult. Christie, Phatak, and Olney (1935), in studying the effect of acacia on the physical-chemical properties of the blood, found that it not only led to a decreased hemoglobin, but coated the red cells and interfered with their respiration. The effect of this coating in preventing accurate cross-matching of blood for transfusion is well known. In such cases either a universal donor must be used or the blood drawn for testing before gum acacia administration.

Another unfavorable report was made by Studdiford (1937), who collected several adverse accounts from the literature as well as reports of several deaths following the use of gum acacia at Bellevue Hospital. Three of the latter cases formed a group with a syndrome characterized by cyanosis, dyspnea, tachycardia, and pulmonary edema. Autopsy was performed in 2 cases and 1 of these showed an extensive destructive

lesion of the liver. In all, 6 serious reactions with 4 deaths occurred in the Bellevue series of 56 patients receiving gum acacia. Studdiford concluded that acacia may result in serious liver damage and also tends to cause serious disturbances of the erythrocytes, interfering with normal gaseous exchange, increasing the tendency to rouleaux formation, accelerating the sedimentation rate, and causing a conglutination of the red cells with the possibility of capillary blockage.

He concluded: "Hemorrhage and shock can be treated more safely by the use of the simpler saline or glucose infusions in combination with transfusion. The possibility for harm is less than with acacia solution. The only indication for the use of acacia solution intravenously in the treatment of shock and hemorrhage is as a last resort when transfusion is unavailable."

Not only is the danger of acute liver damage an important one, but the possibility of chronic acacia deposition is to be considered. Dick, Warweg, and Andersch (1935), as mentioned above, reported finding a considerable amount of acacia in the liver of a child dying some time after infusion.

It is definitely recognized that these maltoward reactions are much more apt to occur after using inferior or deteriorated samples of acacia, Bayliss (1922) stating that all reactions were due to faulty technique. The fact, however, that many of the most recent adverse reports concern reliable preparations properly administered causes one to question seriously the value of giving acacia except when blood is not available.

Hall (1938) performed experiments, concluding: "Repeated intravenous injections of gum acacia solution in dogs have resulted in evident damage for carbohydrate and serum protein metabolism functions of the liver. These changes were shown by glucose and galactose blood sugar tolerance curves and determinations of the plasma proteins. Alteration of the clotting mechanism of the blood, especially the lowered fibrinogen content, has resulted in failure to clot, or in formation of small, fragile and fibrous clots and in a longer bleeding time. The removal rate of bilirubin injected into the blood was unaffected."

Cattell and co-workers (1939) opposed the use of acacia. Saslow (1939) found the colloid osmotic pressure of samples of 6 per cent acacia in 0.9 per cent sodium chloride to vary from 246 to 260 mm. H_2O at 20° C. This closely approximates the average value for human serum of protein concentration ranging between 6 and 8 per cent which was 276 mm. H_2O.

Recent observations of Kendrick, Keeton, and Foley (1938) showed that, when an amount of 12 per cent acacia solution in 0.85 per cent sodium chloride approximating the plasma volume is injected in dogs, there is an immediate increase in blood volume (22 to 30 per cent) and a decrease in the serum proteins. The value for serum acacia plus

protein about equals the original value for serum protein. After repeated injections, the acacia is progressively deposited in the liver as shown by periodic biopsies, gradual increase in liver size, and tissue analyses. In one animal the liver was five times normal size, and of the 756 Gm. injected, 450 (58.8 per cent) were recovered from the liver. These authors concluded that the diminution of serum proteins is not to be regarded as an index of failure of the proteogenic function of the liver, but rather as due to a displacement of the proteins by the acacia.

In conclusion it seems that, while acacia may be of benefit, there are other more perfect blood substitutes. Plasma has almost the portability and storability of acacia without its side reactions.

d. *Ascitic Fluid.*—Davis and White (1938) used human ascitic fluid in the treatment of experimental secondary shock. This work was reviewed in the current comment of the *Journal of the American Medical Association* for the same year. Choisser and Ramsey (1938) also performed experiments on the use of ascitic fluid. They produced shock in dogs by trauma, hemorrhage, or a combination of the two, and treated it with human ascitic fluid. Although they called the shock they produced "primary," this really makes little difference, as they apparently were dealing with what most other workers call "secondary" shock. Nineteen specimens of ascitic fluid were used, the majority of which were obtained from human cases of advanced portal cirrhosis. These authors stated that this fluid varied in protein content from 2.1 to 4.2 mg. per cent. They probably meant grams per cent. All fluids were found to be not only sterile but bacteriostatic. Favorable results were obtained only when fluids devoid of agglutinins were used. The effect on shock was immediate and prolonged. The amount of blood pressure rise was much the same as that obtained with whole blood. In a more recent paper, Choisser and Ramsey (1939) reported that ascitic fluid could be freed of agglutinins and rendered safe for intravenous use in relief of experimental shock in dogs, without necessity for preliminary cross-matching. They accomplished this by a process of electrodialysis, adjustment of pH, and subsequent Berkefeld filtration.

More recently Mulder, Davis, and Streeter (1939) have applied the lyophile principle to ascitic fluid. The dried ascitic fluid redissolved readily and was used in various concentrations, usually about two and one-half times the original. Cross-agglutination tests were used and the fluid administered experimentally to dogs which were in shock as a result of bleeding. The animals usually recovered with return to normal of the blood pressure and oxygen consumption. The plasma proteins fell temporarily. So far, this type of therapy has not been applied to human beings.

e. *Whole Blood. Blood Transfusions.*—The entire history and present status of this most important item in shock treatment have been so well outlined by Vary in his recent review in SURGERY (1940) that only a few

points will be mentioned here. I must partially disagree with one statement in Vary's excellent article where the latter says that cadaver blood found wide usage in Moscow until 1936 when placental blood began to be used. When I visited Moscow in June, 1939, cadaver blood was still widely used, at least in the Institute Sklifassovsky (Central Emergency Hospital). The excellent review of Amberson on blood substitutes (1937) should also be consulted. Other excellent reviews of the use of blood transfusion are those of Lewisohn (1934), Fell (1938), Tuohy (1938), Grimberg (1939) (use in France), and DeKleine (1938) (use by Red Cross). The advantages of transfusions in pneumonia have been reviewed recently by Whitaker (1939), who makes a point that the danger of overloading the heart has been grossly exaggerated.

Heister (1750) suggested blood transfusions as a treatment in shock cases. John Hunter also suggested their use. Crile (1910) advised blood transfusions by the direct method in the treatment of shock. Over twenty-two years ago Blem, of Los Angeles, used to carry citrated blood to places over seventy miles away from that city, this being the first application of the stored-blood principle. Transfusions have been especially useful in preventing shock after neurosurgical operations, as reported by Bird (1929) and other authors. Transfusions have been favored by numerous writers, such as Orr (1934), W. Hunter (1935, 1937), Hume (1938), and Hamilton-Paterson (1939), to mention only a few. Another solution used by Hunter (1935), of Newcastle, had the following composition: ephedrine hydrochloride, 0.060 Gm.; glucose, 30 Gm. (or 5 per cent); gum acacia, 35 Gm. (or 6 per cent); and distilled water, to one pint. Hunter (1937) wrote considerable concerning the use of blood transfusions in obstetric shock. The increasingly important role of transfusions is shown by their popularity. At the Mayo Clinic in 1937, the number of transfusions was 2,805, and of these 36 were 1,000 c.c. or more. In contrast to these figures, during the twenty-two-year period, 1916-1937, a total of 22,937 transfusions was given, an average of a little over 1,000 a year. In 1938, 3,295 transfusions were given, and in 1939, 3,723 (Lundy, Tuohy, Adams, Mousel, and Seldon, 1940).

Various innovations in the technique of transfusions are numerous. The use of *autotransfusion* in the treatment of a wound of the heart by Watson and Watson (1936), of Pittsburgh, is an example in kind. These authors also collected all cases of autotransfusion for various conditions from American literature, finding 272 such cases and adding 2 of their own. Nonfatal reactions were reported in 9 cases (3.3 per cent) and death in 4 (1.5 per cent). The Watsons believed that the possibility of using hemolyzed blood is the chief danger rather than bacterial contamination. The technique of obtaining and administering blood as used in wartime hospitals in Great Britain has been presented by Stewart (1940), of the Royal Infirmary of Edinburgh.

Transfusion Reactions: Seed (1938) reported an incidence of 6.76 per cent reactions following the use of 1,196 transfusions of preserved blood. These could be separated as follows:

Immediate reactions (within 30 min.)	34%
Delayed reactions	49%
Jaundice reactions	11%
Urticaria reactions	6%

In about 5,000 transfusions at the Cook County Hospital 3 deaths occurred. Fell (1938) reported an incidence of 11.6 per cent reactions following the use of fresh blood in 500 transfusions at the Presbyterian Hospital, Chicago. No deaths occurred, but in another Chicago hospital 6 deaths followed 525 transfusions.

Watson and Sanders (1941) of Memphis pointed out that their transfusion reaction rate in a series of 1,600 transfusions had markedly decreased in the past few years. From 1926 to 1935 the reaction rate per transfusion was 17 per cent, while from 1935 to 1940 it was 2.2 per cent. Seldon (1941) of the Mayo Clinic has recently described a device for warming cold refrigerated blood. Stetson (1940) in his recent review of blood transfusion opposes the use of preserved blood. To prevent the occasional occurrence of urinary suppression after intravascular hemolysis following blood transfusion, Bushby, Hart, Kekwick, and Whitby (1940) of the British Army Blood Transfusion Service have several suggestions. These authors believe that suppression of urine in such cases is due to renal tubular obstruction with hemoglobin products. The conditions necessary for its prevention are a high urinary output of at least 1,500 c.c. per day and a constant urinary reaction of pH 6.4 or over. Fluids and alkalies by mouth or vein best fulfill these aims.

Experimental studies have been made by Iljin (1935) and Kunz and Weber (1935). The Russian workers, Petrov, Filatov, Bogomolova, and Stroikova; Wesselkin, Lindenbaum, and Kartaševskij; and Minceev (1935), have studied the nature of hemolytic shock accompanying blood transfusion. They found an increase in the potassium content of the recipient's serum accompanying such reactions.

Massive Transfusions (Adequate Transfusions): It has long seemed to me that there is no more reason why every transfusion should be standardized at a pint than that every diabetic patient should always receive ten units of insulin. A statement by Lundy, Tuohy, and Adams (1938), from whose report the above Mayo Clinic statistics were obtained, substantiates this view. These authors stated:

"Blood transfusion has come to have a different meaning to some of us than to the average person. Previously because a donor could donate 500 c.c. of blood without untoward result, 500 c.c. as a transfusion came to be considered as a full transfusion. We would like to change

this conception so that it would be more commonly considered advisable in doing a transfusion to administer that amount of blood, whether it is 250 c.c., 500 c.c., 750 c.c., 1,500 or 2,000 c.c., so that the patient may be adequately provided with blood."

I would like to paraphrase freely a portion of the above quotation: "A standard pint transfusion is chosen more to fit the donor than the patient; an ideal adequate transfusion should be chosen to fit the patient and several donors should be used when necessary."

Lundy and associates (1938) also stated that "the results that have been obtained with the so-called massive transfusion in certain instances have been dramatic." They, however, believe that Marriott and Kekwick's system is too elaborate and devised a modified method of intermittent small transfusions. McNealy (1938) also deplored the "ritualistic" use of always a pint transfusion.

The reports of Marriott and Kekwick (1935, 1936) are of importance in that they pioneered in directing attention to the necessity for fitting the size of the transfusion to the needs of the patient. Using a visible drip with citrated blood, they avoided settling of the cells by bubbling a slow stream of oxygen through the suspended donor flask. Their cases included bleeding peptic ulcers to a large extent and they gave blood at a usual rate of forty drops per minute (130 c.c. an hour) until the anemia was controlled. The following data concerning the eighty-seven drip transfusions carried out by them at the Middlesex Hospital, London, during 1935 may be of interest:

Total number of transfusions	87
Total volume of blood drip transfused (excluding citrate)	233.5 L.
Total duration of these transfusions	2,545 hr.
Average drip transfusion	2.7 L. (= 5 pt.)
Average duration of each drip transfusion	29 hr.
Largest single transfusion	6.3 L. (= 11 pt.)
Longest single transfusion	62 hr.

In an editorial DeBakey (1938), of Ochsner's clinic, opposed the suggestion of Marriott and Kekwick concerning continuous drip transfusions. A closer perusal of this editorial indicates, however, that DeBakey merely opposed citrate transfusions in general. He favored large transfusions when necessary and has given as much as 7 liters of unmodified blood in three or four days. He practically denies the possibility of "speed shock" and has transfused "not infrequently" as much as 650 c.c. in three minutes.

Stored Blood. The "Blood Bank": Bureeva (1935) described the blood bank system in Leningrad at the Research Institute for Blood Transfusion under the leadership of (the late?) Prof. E. Hesse. As Fantus (1938) pointed out, the idea of calling a blood collection a blood bank and making it function like a blood bank originated at the Cook

County Hospital in Chicago. The technique used at this institution has been described by Schirmer (1938). Exact details of blood preservation technique and conduct of a blood bank are given by Fantus and Schirmer (1938). Blood banks are called blood depots in England.

Lewisohn (1938) wrote opposing the method used at the Cook County Hospital. This author pointed out that by the technique used at that institution the patient does not receive pure blood, but blood diluted in equal parts with normal saline solution. He pointed out that such dilution is entirely unnecessary and may diminish considerably the benefit obtained in many cases. Cotter and MacNeal (1938) advised buffering the sodium citrate solutions used for blood preservation with citric acid solution. The use of bank blood was discussed by Goldstein, Olsman, and Edlin (1939). Novak (1939) found experimentally that, with the possible exception of sulfanilamide, bacteriostatic drugs are not useful in blood preservation.

Cameron and Ferguson (1939) have recently summarized their experiences with 1,000 transfusions from the blood bank of the Philadelphia General Hospital. The blood is given undiluted, contrary to the Cook County Hospital practice. It is interesting that only 25 of 1,123 deposits in the bank (2.2 per cent) were discarded because of age. The remaining 98 specimens were not used because of unsuitability (seropositive, 53; hemolyzed, 17; infected, 6; etc.). Discarding was done at five weeks, but the demand, especially for the commoner blood groups, was so great that the average flask remained in the refrigerator only five days. A total of 7.4 per cent of the transfusions had reactions.

De Gowin, Harris, and Plass (1939) studied the plasma potassium in stored blood, finding it to increase considerably. De Gowin, Hardin, and Harris (1940) studied the toxicity of blood with high plasma potassium when used for transfusion into human beings. They concluded that when given slowly such blood was not toxic and that "the concentrations of plasma potassium encountered in blood stored for one month are not high enough to cause significant increases in the serum potassium of the recipient." It is of interest, however, that all of the recipients in the cases of De Gowin and associates had normal values before transfusion. Whether this same conclusion as to the nontoxicity of high potassium blood would apply to patients already with high potassium levels is to be considered. De Gowin, Harris, and Plass (1940) extended these ideas in their comprehensive review of the use of preserved human blood.

De Gowin, Harris, and Plass (1940), of Iowa City, found that the blood preservation solution giving the least hemolysis included: ten volumes of blood, thirteen volumes of 5.4 per cent anhydrous dextrose in water, and two volumes of 3.2 per cent dihydric sodium citrate in water. At the end of a month's storage, blood in this dextrose-citrate mixture had hemolyzed only from one-twenty-fifth to one-fiftieth as much as did blood in citrate solutions alone or in citrate-saline mixtures.

Advantage of Glucose in Preserving Fluid: Numerous writers have found that glucose tends to preserve blood better than a simple inorganic solution. Kolmer and Howard (1940) found that blood is better preserved by the addition of dextrose (modified Rous-Turner, 1917) or of dextrin (Maizels and Whittaker, 1939, 1940) than by plain citrate or the Moscow Institute of Hematology methods. Aylward, Mainwaring, and Wilkinson (1940) and Dubash, Clegg, and Vaughan (1940) also reported that citrate-glucose seemed to be the best preservative for blood, inhibiting, although not preventing, the increase in plasma potassium. Maizels and Whittaker (1940) working at the Emergency Blood Transfusion Center, Maidstone, England, advise a more dilute mixture than that suggested by De Gowin, Harris, and Plass (1940) (*vide supra*). They think their solution is more isotonic and use a solution of sodium chloride (0.5 per cent), sodium citrate (1.05 per cent), and glucose (1.0 per cent).

Changes in Stored Blood: The interesting observations of Levine (1940) on the length of life of a transfused red cell in the recipient indicate one of the objections to the use of stored blood. Identifying the donor cells in the patient by means of the group specific factors M and N, he found that cells stored 3, 10, or 14 days survived for 80, 60, or 20 days, respectively, as compared with the survival time of 95 days for fresh cells. Two of the best recent reviews on the changes in stored blood are those of Bull and Drew (1940) and of Scudder (1940).

Mainwaring, Aylward, and Wilkinson (1940) found that the potassium content of plasma from two-week-old stored blood contained 116 mg. per 100 c.c. This suggested to them, as it has to others, the possibility of toxic reactions, and they advised early separation of the plasma from the blood and slow administration where high potassium plasma had to be used. The studies of the English workers, Downman, Oliver, and Young (1940) at the Emergency Blood Transfusion Depot, Sutton, also indicated an increase in potassium of stored blood. The blood was stored at 2 to 4° C. according to Medical Research Council specifications (one volume of blood to one-half volume of 1.05 per cent sodium citrate in 0.85 per cent sodium chloride). During the first week the plasma potassium concentration rose rapidly to between five to ten times the initial level; thereafter the rise was comparatively slow. The potassium came from the red cells, its liberation being quite independent of hemolysis. Macdonald and Stephen (1939) also discuss the changes in stored blood, especially the decrease in number of erythrocytes.

Quick (1940) and Ziegler, Osterberg, and Hovig (1940) reported a decrease in the prothrombin content of preserved blood. While this is of interest, it is not a serious deterrent to the use of preserved blood in shock conditions. Warner, De Gowin, and Seegers (1940) also found a decrease in the prothrombin content of stored blood, the value reaching the 50 per cent level at the end of about three weeks. Observations on

changes in human blood stored at 4° C. were made by Lipp and Hubbard (1940).

Rate of Transfusion: Some aspects of this subject have already been described under the heading "Massive Transfusions." In a more recent article Marriott and Kekwick (1940) stated: "In every transfusion the volume of blood to be administered and the rate of its administration should be matters of primary importance. The custom of giving a transfusion, meaning about a pint of blood in half an hour, is irrational and unsatisfactory." This particular article is devoted to a consideration of transfusion for the relief of anemia uncomplicated by hemorrhage, and for this purpose they advise adequate transfusions. Once the required rise of hemoglobin has been settled for any case, the volume of blood in cubic centimeters needed may be calculated as follows:

$$\frac{\%\text{ rise of Hb. required}}{100} \times \text{Patient's normal blood volume in c.c.}$$

The blood volume may be roughly determined as 40 c.c. per pound body weight.

Marriott and Kekwick again emphasized the importance of slow calibrated administration by the drip method that they advised five years ago (1935). In a series of massive transfusions to 177 adults, 67 of whom were over 50 years of age and 35 over 60 years of age, almost all these patients showed no symptoms of cardiac embarrassment. The average volume of blood (exclusive of citrate) given in the 177 transfusions was 2,039 c.c.; in 21 cases it was more than 3,000 c.c. All transfusions were given very slowly; the average duration was 27.1 hours, with an average rate of 84 c.c. per hour (since the average volume of *citrated* blood was 2,285 c.c.). The slight distress present in 5 cases quickly disappeared in 4. One of the advantages of slow administration is that, if cardiac failure does develop, there is adequate time to recognize it. The one death occurred when a transfusion was done in a private dwelling. These authors finally postulate that these slow transfusions for anemia allow time for the excess plasma to leave the blood stream. They advise that the rate not exceed fifty drops per minute for the average-sized man.

It seems that this rate limit may be desirable in chronic anemia cases but not advisable in acute shock or hemorrhage cases. If a patient has just lost 1,500 c.c. from a severed vessel, it seems hardly necessary to take nine hours to restore that blood. Theoretically it would seem that the more rapidly the blood or plasma has been lost the more rapidly may it safely be replaced, provided such restoration is begun promptly.

Marriott and Kekwick (1940) in a later note point out that, while they believe that in chronic anemia with no marked decrease in blood volume slow transfusions are necessary, in shock with lowered blood volume very

rapid transfusions may be necessary. Thus, a pint may be given in fifteen minutes or the rate may be even faster in severe cases.

Placental Blood: Fine, Alter, and Baptisti (1940) summarized their experiences with the use of placental blood for transfusion at the Baltimore City Hospital. The use of such blood seemed theoretically attractive, but they concluded that it was impractical, chiefly because of contamination of a high percentage of specimens.

Red Cell Infusion: While many articles have been written on the use of plasma, few have appeared on the subject of cell infusion. One of these latter is the paper of Beumer and Schwartzer (1939) recommending the use of plasma-free cells in anemia. The use of blood cell concentrated suspension for anemia was also discussed by MacQuaide and Mollison (1940).

Hemoglobin-Ringer Solution: While this is, strictly speaking, a crystalloid solution, it will be discussed at this point. The recent review of Fairley (1940) on the fate of extracorpuscular circulating hemoglobin in man is of interest as well as the work of Amberson (1937) in this connection. The use of hemoglobin-Ringer's solution clinically in four patients with anemia was reported by O'Shaughnessy, Mansell, and Slome (1939). After preliminary alkalinization of the urine, amounts of 600, 200, 250, and 1,000 c.c. of 5 per cent solution were given intravenously in an hour or less to the four patients respectively.

Recent Publications: Recent papers on blood transfusion are many, especially in the British medical press. Reviews include those of Du Bois and co-workers (1940), Douglass (1940), Ravitch (1940) on the technique of the blood bank in the Johns Hopkins Hospital, Wilson and Jamieson (1938), Bull and Drew (1940), and De Gowin and Hardin (1940) on preserved blood. Hammond's recent (1940) remarks seem to be unique in casting doubt on the value of blood transfusion.

The use of sulfanilamide as a preservative of stored blood was studied by Novak (1939) and Hunwicke (1940). The latter reported that the concentration suggested by Novak (1:5,000) was not adequate and advised a 1:1,000 dilution. This higher dosage would mean 0.5 Gm. of sulfanilamide in each 500 c.c. blood transfusion. This dose is not large. The sulfanilamide must be dissolved in about 12 c.c. of warm water before mixing with the blood. Other techniques of preparing, storing, and administering preserved blood include those of Elliott, Macfarlane, and Vaughan (1939), and of Boland, Craig, and Jacobs (1939). Corelli (1940) advised a proprietary Italian thiosulfate preparation as a blood preservative, *"Novotrans."*

Diggs and Keith (1939) in two articles summarize their experiences during the first year of using a blood bank at the John Gaston Hospital in Memphis. In a series of 1,415 transfusions there was a reaction rate of 6.7 per cent and 5 deaths. They advise a test for hemolysis just before using all preserved blood samples. This is important because the detec-

tion of hemolysis by looking at the blood in a flask is unreliable, for it may appear to be hemolyzed when it is not, or the supernatant layer may be clear even when there is gross hemolysis in the cell layer. Edwards and Davie (1940) gave an account of the first 1,500 bottles of preserved blood distributed by the Merseyside War Blood Bank. Similar to the practice at the John Gaston Hospital, Memphis, they use the blood left in the taking tube in testing for Wassermann reaction, etc. Five per cent reactions (rigors) occurred following the giving of the blood. In a series of 951 transfusions, De Gowin and Hardin (1940) found 3.68 per cent reactions.

The "closed citrate method of collecting blood" used by Diggs (1940) at the blood bank of the John Gaston Hospital, Memphis, has several advantages in simplicity. Eliminating mechanical suction devices, the blood is allowed to run downhill into a single sterile bottle containing citrate. The blood left in the tubing at the completion of the procedure is collected and utilized for serologic tests and for typing and cross-matching.

Besides the danger of incorrect typing and cross-matching there is always the danger of intragroup reactions in the blood transfusion as pointed out by Wiener and Peters (1940) and others. Knoll and Schürch (1938) reported on the use of heparin in blood transfusion. Heparinization of the donor seemed to exert no ill effect on him or on the recipient.

Stead (1940) studied the collapse following sudden removal of large amounts of blood from professional donors kept in the horizontal position. After removal of 760 to 1,220 c.c., five of the six donors developed collapse when from 15.5 to 19.7 per cent of the total blood volume was removed. The collapse was accompanied by tachycardia and sweating of the forehead and coolness of the hands and feet. In the early stages there were no cerebral symptoms, the supply of blood to the brain being adequate. The onset of the collapse was sudden with a sharp blood pressure fall to 50 mm. Hg or below. At the height of the reaction there were bradycardia, nausea, and blurred vision.

The idea recently expressed in an article in the French literature by Bécart (1939) that all transfusions should be given rhythmically, i.e., by means of an artificial "heart" with intermittent pulsatile pressure, has not been widely adopted. Bécart believes that the manner of injecting is as important as the substance injected. Another type of transfusion is the continuous reciprocal method as used by Duncan, Tocantins, and Cuttle (1940).

Glinskiy (1940) found that warming did no good in blood transfusions. In using unwarmed (10 to 20° C.) blood there were 26.1 per cent reactions, while in a previous group of 1,400 transfusions of prewarmed blood there were 38 per cent reactions.

Cooksey (1940), in discussing the blood bank at Harper Hospital, Detroit, stated that all blood is converted into useful plasma when it is seven days old. Whole citrated blood is used, and following administration of the first 700 bottles of blood from the bank, only eight reactions occurred, most of them being very mild. This low incidence of reactions is in marked contrast to that of previous years with fresh blood.

The recent symposium on blood banks at the Detroit Regional Meeting of the American College of Surgeons, April 1, 1940, brought forth several interesting points. E. H. Schirmer reported on three years' experience with the Cook County Hospital blood bank. In 1936, before instituting the bank, there were 7 per cent reactions. Last year in a series of 6,446 transfusions there were only 1 per cent. She stated that they still use the sodium citrate-saline solution as they believe the De Gowin glucose solution favors hemolysis. The blood is given at the rate of 40 to 60 drops per minute. W. B. Cooksey stated that there was only one reaction in the last 407 bank blood transfusions at Harper Hospital, Detroit (0.25 per cent). Scudder emphasized four points to be remembered in using a blood bank: (1) chemical cleanliness, (2) rapid turnover of specimens, (3) slow administration, and (4) narrow plasma-cell interface in preserving flasks.

The disadvantages of stored blood would seem to rest in deterioration, largely from diffusion of electrolytes such as potassium and magnesium from the cells into the plasma. This is especially rapid when blood is transported and this again limits the use of stored blood. Scudder (1940) remarked in this regard: "In hemorrhage and shock, when the need for blood is the most urgent and where preserved blood might find its chief usefulness, its improper use would seem to carry the greatest danger." It would seem that most of these objections to stored blood could be obviated by using stored plasma.

Cadaver Blood: The use of cadaver blood in the treatment of shock was introduced by Dr. Skundina, a female assistant of Prof. Serge S. Youdine (Judin, Yudin),* of the Institute Sklifassovsky (Central Emergency Hospital), Moscow. Youdine (1936) reported further on the use of cadaver blood. It was given a brief trial in actual practice at the Philadelphia General Hospital. Moore (1938) reviewed the use of cadaver blood in Chicago and an editorial in the *Journal of the American Medical Association* (1938) reviewed the entire subject.

In June, 1939, I spent two days with Professor Youdine and watched the entire setup and use of cadaver blood transfusions. The choice of cadavers is one of the most important items. Youdine manages all the emergency cases in Moscow, controls all the ambulances, and has three telephone operators working night and day answering emergency calls only. He thus has an enormous amount of material to choose from. A total of 1,054 cadavers were used in the three-year period 1935-1937.

*Professor Youdine told the writer that he prefers this spelling, believing it to be a more accurate translation of the Russian alphabet.

A total of 1,738 liters of blood was obtained and of this 228 liters were discarded because of positive Wassermann reaction or other diseased condition. The average blood per cadaver was 1,650 c.c. and the average time after death that the blood was obtained was two and one-half hours. Some of the cadavers were traumatic cases:

	CADAVERS	USED
Fracture of skull	22	15
Gunshot wound of head and thorax	9	8
Closed thoracic trauma	16	10
Combined trauma	20	12
Buried in earth	7	6
Electrocution	34	29
Total	108	80
		74%

But by far the largest part of the blood was obtained from patients with angina pectoris. Youdine gets 10 to 15 male deaths from angina pectoris a day! Of the angina pectoris deaths 74 per cent are males and these make the best cadavers, rarely having a positive Wassermann. To show how many cadavers are discarded: in 1932 to 1934, of 5,104 cadavers transported by Youdine's ambulances, only 1,432 (28.5 per cent) were brought to the hospital for use, the others being taken directly to the morgue.

In obtaining the blood it is best to wait 1 to 3 hours after death but not more than 6 to 10 hours, the time being less in warm weather. The cadaver is placed on a table in Trendelenburg position, the neck sterilized with iodine, and the cadaver draped with sterile sheets. The operator wears sterile gloves and gown. With sterile instruments the external jugular vein is exposed and two glass tubes are inserted. These are 0.75 in diameter and 15 cm. long. A straight tube is placed toward the thorax and a right-angled tube toward the head. The blood is allowed to flow by gravity into sterile containers. It is then placed in a refrigerator and the process of fibrinolysis occurs spontaneously after clotting. It is this process that was Skundina's great discovery in 1930. Cadaver blood was first used on March 23, 1930.

In a series of 1,157 transfusions with cadaver blood there were 214 reactions (18 per cent) with 0.2 per cent deaths. All 3 deaths occurred in cases where a small transfusion of only 250 c.c. blood was used. The time of storage up to thirty-five days seemed to make little difference in the reaction rate. Youdine is such a firm believer in transfusion that he told the author: "The vein is for transfusion." The subject of blood transfusion will be discussed below under the heading "Shock in Wartime."

(To be concluded in the April issue. The references will accompany the last section.)

Review of Recent Meetings

REVIEW OF THE FIRST MEETING OF THE SURGICAL INVESTIGATIVE SOCIETY OF THE SOUTH, OCT. 6 AND 7, 1940, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, NASHVILLE, TENN.

MICHAEL DEBAKEY, M.D., NEW ORLEANS, LA.

(From the Department of Surgery, Tulane University School of Medicine)

THE Surgical Investigative Society of the South has been organized from a group of southern surgeons. The purpose of the organization is to band together a small group of contemporaries, interested in surgical progress, and by annual meetings at some medical center to exchange ideas and to see for themselves the advances and research, in progress.

"The first meeting was held at Vanderbilt University in October. The first day was given over to procedure of organization and to a general discussion, initiated by the members themselves, as to researches being conducted by them and at their particular home locations.

"Officers elected were: **Dr. Ira A. Ferguson,** Atlanta, Ga., president; **Dr. Michael E. DeBakey,** New Orleans, La., vice-president, and **Dr. Henry Poer,** Atlanta, Ga., secretary-treasurer.

"The next meeting is to be held in Baltimore in October, 1941.

IRA A. FERGUSON, President."

Samuel McLanahan, Baltimore: **The Use of Sulfanilamide, Sulfapyridine, and Sulfathiazole on the Surgical Service of Johns Hopkins Hospital** (abstract*).—With the development of new derivatives in the sulfanilamide group, the indications for and use of these drugs are undergoing constant change. Sulfanilamide, however, continues to hold its place in the treatment of hemolytic streptococcal infections. In Welch bacilli infections it has proved effective clinically. Especially has it been used prophylactically in compound fractures and other open wounds. Introduced locally in the wound it has apparently been effective and has not interfered with wound healing.

Sulfapyridine was a welcome addition to the series, but in actual practice it is being replaced very largely by sulfathiazole. The latter drug is less likely to produce nausea but more likely to produce a rash and the troublesome drug fever.

In abdominal surgery, sulfathiazole is achieving special success. Recent reports by A. F. Jonas indicate its effectiveness in treating and preventing peritonitis. It has been given as a routine measure in the postoperative treatment of ruptured appendicitis and abdominal trauma, and as a preoperative measure in operations upon the colon. The sodium salt, not yet available commercially, has

*Reports of papers so designated are abstracts prepared by the indicated authors themselves.

frequently been employed for intravenous use. Rectal strictures due to lymphopathia venereum have responded to sulfanilamide, sulfapyridine, and another drug, sulfanilic acid.

The future gives promise of the development of new compounds, one of which, sulfanilylguanidine, has already been reported by E. K. Marshall and his associates. This drug is poorly absorbed and so remains in high concentration in the intestinal tract. Its bactericidal effect upon diseases of the intestine and upon the intestinal contents is being carefully investigated. Doubtless much more will be heard of this drug in succeeding months.

Discussion: **Gaston Gay,** Atlanta, asked McLanahan what experience he has had with giving sulfathiazole per rectum. He reported three cases of peritonitis in which it was difficult to give the drug by mouth. One patient who received sulfathiazole had a rise in temperature and diarrhea following the use of the drug. **Ambrose H. Storck,** New Orleans, stated that he and his associates had anticipated and planned to use these drugs in gunshot wounds, but it so happens that the incidence of gunshot wounds had decreased. He expressed the opinion that the use of sulfanilamide in the form of hypodermoclysis, as suggested by Ravdin, has been of distinct benefit in their experience. **William H. Prioleau,** Charleston, S. C., agreed with McLanahan's statement about the use of sulfanilic acid in rectal strictures. In Charleston they have had quite a large series of these patients and they have been reviewed by **Edward Parker,** former resident surgeon in Vanderbilt Hospital. His findings are in absolute agreement, that the patients are more comfortable, the discharge is less, but the physical characteristics remain about the same. They have had about twenty of these patients of all kinds under observation. **Michael DeBakey,** New Orleans, directed attention to the use of these drugs in gas bacillus infections. He referred to some investigative work done in the Department of Experimental Surgery at Tulane University by A. B. Longacre. It was found that in *Clostridium welchii* infections in guinea pigs these drugs were of little, if any, value. Although their clinical experience was limited, it was their opinion that the drug has not been of definite value in these cases. However, he emphasized the fact that it was difficult to evaluate results of therapy in these infections, because of the numerous factors involved. **D. Henry Poer,** Atlanta, asked if some side results which might be dangerous had been observed in the use of sulfathiazole and sulfanilylguanidine. Because these drugs are being used so commonly, it would be worthwhile to direct attention to any untoward effects which they might produce. **Richard T. Shackelford,** Baltimore, mentioned one other type of case in which it was very useful; that is as a prophylactic in resection of the jaw. Resection of the jaw is in the mouth, a very dirty field. He has used sulfanilamide six times with large resections of the jaw. The wound in each case healed per primam. Sulfathiazole was used the last four times and in each case the wound healed per primam. **Clarence E. Gardner,** Durham, N. C., asked if there is any ill effect from the preoperative use of the drug from the standpoint of anesthesia or from the standpoint of wound healing in resection of the jaw. **George T. Wood,** High Point, N. C., stated that recent experiences with sulfathiazole tempted him to see how much protection could be obtained from the preoperative administration in acute inflammatory pelvic conditions. Two weeks ago a case was seen with acute pelvic peritonitis, with temperature of 103 to 104° F. The patient was extremely sick. After three days' administration of sulfathiazole, there was a drop in temperature, a diminution in vaginal discharge, and a diminution in the abdominal pain. Eight days after the administration of the sulfathiazole, the patient was operated upon. The postoperative reaction was much less severe than is usually present. **Ralph M.**

Larsen, Nashville, Tenn., stated that he and his associates have had a moderate amount of experience with sulfanilamide, extending for a period of eighteen months. They have treated sixty-eight cases of lymphopathia venereum. It has been very definitely shown in that group that there is almost complete disappearance of the inflammatory reaction. Colostomy was done in about 5 per cent. The average gain in weight of those treated with sulfanilamide has been somewhere in the neighborhood of 50 per cent. In general, the inflammatory reaction has failed to recur even after sulfanilamide has been discontinued for six to nine months, except in those instances where there is marked persistence of the stricture. The greatest benefit received from it was in early lymphopathia venereum. He did not know how many early acute cases there are in this study. Their experience has been that given an early case with proctitis as an initial lesion, with extensive edema and early ulcer, it can be healed with no stricture whatever if the patient is placed on sulfanilamide and if necessary given a temporary colostomy. He had recently seen a case which brings up the question as to whether or not in the presence of pneumococcus infection or compound fracture one would give sulfathiazole in the light of the evidence at the present time that sulfathiazole is not readily excreted by the choroid plexus.

Regarding Gay's question about the rectal administration of the drug, **McLanahan**, in closing, admitted that he and his co-workers have had no personal experience nor do they know of any experience in the rectal administration of sulfathiazole. The fact is the intravenous drug just happens to be available. The rectal administration would be certainly very important to follow. They have not seen diarrhea accompanying the drug, but a patient occasionally may get it. As regards Welch bacillus infection, it was his understanding that Welch bacilli many times are mixed up with streptococcus, and some of the effect of treatment may be because streptococci may be present in the infection in the laboratory animal. From clinical experience with a number of cases it was his opinion that many times amputations have been avoided. However, there are many things one can do for such patients and he thought all should be done as far as possible. In regard to side reactions, as mentioned by Poer, complications can be listed in eight different groups. In addition to the two mentioned, drug fever and rash, there are blood changes which are familiar and which should be looked for. It demands careful observation of the blood picture. There may be jaundice. There may be psychosis, which he had observed in a child receiving sulfathiazole. The child was completely disorientated and confused. These are among the important side effects. As regards Wood's remarks about pelvic irritations, their resident had observed a series of appendical cases in which these drugs were used. It was found that the wound heals much more promptly, there is less discharge, and there is a cleaner looking wound and fewer secondary abscesses. The resident reported that he and the other surgeons use fewer drains in ruptured appendix, possibly one cigarette drain instead of three, and that the healing is more prompt and the hospital stay shorter. As regards Larsen's remark about the treatment of early lymphopathia venereum, it would certainly be important if it is possible to keep those cases from going on to permanent stricture formation. In regard to head injuries, there are a number of factors to be considered. McLanahan stated that at Johns Hopkins Hospital, W. E. Dandy is experimenting on the application of these drugs in postoperative infections and compound head injuries. He does not think it is effective in brain abscesses, because they are well walled off from the blood supply.

Richard T. Shackelford, Baltimore: **Peritoneoscopy** (abstract).—Peritoneoscopy has been used in Baltimore as a diagnostic procedure since February, 1938.

The examination has been performed in eighty cases and from this experience we believe it is especially indicated to establish the diagnosis in suspected cirrhosis of the liver, metastases to the liver or peritoneum, inoperable carcinoma of the stomach, tuberculous peritonitis, carcinoma and cysts of the ovary, ectopic pregnancy, myomata uteri, and pelvic inflammatory diseases.

We believe that it should not be used in acute abdominal inflammatory disease, abdominal distention, or where many adhesions are known to be present. Furthermore, it should be resorted to only if the usual simpler laboratory procedures have failed to determine the diagnosis.

The limitations of the method must be kept in mind and it should be used only for a specific purpose, as to (1) establish a differential diagnosis, (2) confirm a previous diagnosis, (3) determine the nature, location, and extent of a tumor.

In our series the intestine was perforated in one case, but without any serious effect. There were no other complications. The procedure resulted in an incorrect diagnosis in one instance and was unsuccessful due to adhesions in three others. There were no fatalities.

We believe it is a valuable diagnostic procedure in a small number of selected cases, and in such a group will prevent many unnecessary exploratory laparotomies.

Discussion: **Rawley M. Penick, Jr.,** New Orleans, stated that, although he has had no experience with this procedure, he has not been able to get enthusiastic about it for several reasons. One is that it does have dangers. Another is that it seems to him that one is dealing with conditions that are finally operative. He asked Shackelford if he knew how many of these patients subsequently did have laparotomies. He also made the point that an exploratory laparotomy can be done very easily under local anesthesia. He wondered if more information could not be obtained in this way than with this instrument. He had gotten the impression that it necessitates operation later anyway, so its value is somewhat nullified for that reason. The greatest information is to be found in the liver. **Michael DeBakey,** New Orleans, agreed in general with Penick. Although he has had no personal experience with it, one man in their department had performed the procedure in thirty or forty cases. In this group of cases the procedure had not proved of distinct informative value and in some the findings were definitely misleading. He asked if false information had been given in Shackelford's series. Obviously, usage and experience are important factors. However, it was the general impression that the indications were definitely restricted. **Ambrose H. Storck,** New Orleans, stated that as regards penetrating wounds of the abdomen, Griswold and his associates in Louisville, Ky., have had quite a number of cases of penetrating wounds of the abdomen in which they felt that the use of the peritoneoscope had helped them to recognize a few cases with actual perforation and hemorrhage which otherwise they might have missed. He believed that in acute abdominal conditions it might find a place. In borderline cases, especially in instances of other injuries where abdominal exploration is to be avoided if possible, he was of the opinion that it may be valuable.

William H. Prioleau, Charleston, S. C., agreed with Shackelford that there is a very definite place for it. In fact, they have saved a great many hospital days and saved a certain number of laparotomies. It has been mainly used in a small series for diagnosis of carcinoma, particularly of the ovary, which had not been diagnosed otherwise and in which the patients were not subjected to hospitalization.

Shackelford, in closing, stated that, in answer to DeBakey's question, false information was given in his thirteenth case, curiously enough, and so from that time on it has been his custom not to give information in which there is any reasonable doubt, in which there is actually any doubt. By means of biopsy it is possible to determine with accuracy what is present. If he is not sure of it, it is recorded as undeterminable by peritoneoscopy. That has occurred in three cases which were noted as "unable to determine diagnosis." The instrument should not be used just for general inspection of the abdomen. It should be used to answer only specific questions: Is this carcinoma of the liver or cirrhosis of the liver? Is it metastasis to the liver? Is the spleen enlarged or is it small? If it is enlarged, a biopsy should be made to see what the microscopic picture shows. In other words, it should be used for making differential diagnosis, not just for a general inspection of the abdomen. A diagnosis should not be made unless one is certain. In regard to Penick's question, he did not have these particular figures on the entire 80 cases, but he had the figures on the first 50 cases. In the series of 50 cases they saved 22 exploratory laparotomies. In regard to Storck's remark, he stated that he was familiar with Griswold's work. Their procedure in penetrating wounds of the abdomen is to insert the peritoneoscope and see if perforation of the peritoneum, and not of the intestine, has occurred. He would not trust any opinion one could give as to whether the intestine was perforated by a bullet or a stab wound. One could see, of course, whether there is a hole in the surface of the peritoneum. They have reported 6 cases. There have been 28 instances reported by various authors in which they used peritoneoscopy to determine the presence or absence of hemoperitoneum.

John V. Goode, Dallas, Tex.: **Experiences With a Transverse Abdominal Incision** (abstract).—The disadvantages of the transverse abdominal incision in the upper abdomen are: (1) This incision is not suitable for exploratory procedures. (2) Occasionally the transverse incision is not adequate and the operation must add a midline incision to the transverse incision. (3) The transverse incision takes a few minutes more time than does a vertical incision. (4) The upper portion of the wound is in the way when the operation is one to explore the common duct. (5) If a hernia develops, its repair may be more difficult if it is close to the costal margin.

While these disadvantages are real, they are overweighed by the very real advantages of the transverse incision. The advantages are: (1) The closure is more secure than the closure of the vertical incision because the transversalis abdominis muscle is divided parallel with its fibers and consequently every cough or breath does not tend to pull the wound apart. (2) This incision is more efficient in that all of it is used and not just the upper angle. (3) The transverse colon and omentum keep the small bowel out of the wound. This tends to prevent shock and to prevent adhesions. (4) The exposure is ideal. (5) There is no injury to nerves and consequently no atrophic or weak muscle following this incision. (6) Disruption and hernia seem to be less frequent following the use of the transverse incision. (7) Of great importance is the lessening of pain following this incision. With the freedom from pain there will be deeper respiratory movements, less atelectasis, and less pneumonia.

Discussion: **Michael DeBakey,** New Orleans, directed attention to the lower transverse incision, particularly for appendectomy. In Tulane University surgical service, the transverse incision has been used for a number of years. It has practically all the advantages enumerated for the upper transverse incision. It has the advantage over the McBurney incision that better exposure may be ob-

tained, pelvic exploration can be done, and the incision may be more easily enlarged. This incision is frequently referred to as the Davis incision, but Elliot described it in 1896 (Boston M. & S. J. 135: 433) and Rockey in 1905 (Med. Rec. 68: 779). It is performed by making the incision horizontally on a level with the anterior superior iliac spine, extending from a few centimeters medial to this point to a few centimeters lateral to the midline. The external oblique aponeurosis and the lateral half of the rectus sheath are incised in line with the skin incision, exposing the rectus and internal oblique muscles. The former is retracted medially and the fibers of the latter as well as those of the transversus abdominis are separated. The peritoneal cavity is entered by extending the incision transversely through the lateral half of the rectus sheath and the transversalis fascia. **Paul W. Sanger,** Charlotte, N. C., asked about the wisdom of using silver wire. **James A. Kirtley, Jr.,** Nashville, asked Goode if he uses this incision in many early cases of perforated ulcer.

Goode, in closing, stated that, as far as silver wire is concerned, he adhered to his training in Cincinnati. When he uses silver wire, nothing else is used. In the case of early ulcers he uses only silver wire.

Clarence E. Gardner, Jr., Durham, N. C.: **Certain Observations of the Use of the Digital Oscillometer in the Recognition of Peripheral Vascular Diseases** (abstract).—An instrument was presented which measured the magnitude of pulsations of the arteries of the fingers and toes. It had been made in the instrument shop at Duke University. Charts showing the range of pulsations in the digits of normal individuals at various temperatures were presented. Charts showing the range of pulsations in the digits of patients with Raynaud's disease and also with obliterative vascular diseases were also presented. The ability of the instrument to record changes in pulsations before and after smoking and before and after sympathectomy was demonstrated. It is thought that the instrument will be of value in differentiating vasospastic from obliterative vascular diseases.

Discussion: **John V. Goode,** Dallas, asked Gardner about the width of the cuff, because this is considered significant. As to the degree of oscillation, he also asked if the amount of mercury used to bring it up would have any significance whatever in the blood pressure of the finger. **Samuel McLanahan,** Baltimore, stated that he observed variations of waves in all cases. He asked if one always gets oscillations even though palpable pulsations may be absent. **Michael DeBakey,** New Orleans, emphasized the significance of vasospasm in peripheral vascular disease. Its importance lies in the fact that it forms the one controllable factor from the standpoint of therapy. For this reason it is important to determine not only the presence or absence of vasospasm, but also its extent. For practical purposes an apparatus of simpler construction than that described by Gardner would be desirable. The instrument used in the peripheral vascular clinic at Tulane University has been one similar in principle to one constructed by Roy Turner, of the Department of Medicine at Tulane University. This apparatus is a recording oscillometer, but in its simpler form may be applied clinically without the recording unit, which is the complicated part. **D. Henry Poer,** Atlanta, stated that it seems to him in studying peripheral vascular conditions that in the past we have had certain diagnoses handed to us, such as thromboangiitis obliterans, Buerger's disease, and arteriosclerosis with spasm or perhaps without spasm. On the other hand, a large number of patients are encountered who do not fall into one of these groups, and it seems that this occurs to such an extent that it is difficult to classify them. The instrument described may be of some value in such cases. Another important problem in the treatment of

peripheral vascular disease is the element of smoking, whether it be in the 10-year-old boy he has mentioned or the 60-year-old man. It seems that this is a habit which is very difficult to break and one practical value in an apparatus of this sort is that you can take a man into a constant temperature room and show him the figures so that he can see the temperature changes in his digits or in his toes and also how his oscillations vary in his blood vessels. It might be a very good way to sell a patient on the idea of stopping something that is distinctly harmful.

Gardner, in closing, emphasized Poer's remarks about smoking. They have used this instrument in obliterative disease, arteriosclerosis, and Buerger's disease. In all of them it was found they had no pulsations at all in the digits. As regards McLanahan's remarks, one frequently finds normal pulsations at the wrist and ankle and normal oscillometer curves, but still the patient has disease of the peripheral vessels. It is in such cases that this instrument is helpful. As regards the instrument mentioned by DeBakey, he was of the opinion that it was not of great clinical value. The plethysmograph perfected by Johnson in Chicago is an excellent apparatus. It is very exact and does the same thing as this instrument he has designed. Their difficulty has been in getting the thing to work. The plethysmograph takes a trained technician to make it work and they were not skillful enough or did not have the patience when something was wrong, and so gave it up. It is on the market and is successfully used at this time. The great value of the one he presented is that the whole extremity can be immersed in a water bath. Those working with this know that there are great variations in pulsations. They are not equipped with a constant temperature or constant humidity room and find it easier to immerse the extremities. Goode asked about the width of the cuff, but he stated that he was not enough of a physicist to answer that.

Paul W. Sanger, Charlotte, N. C.: **Demonstration of the Tourniquet Technique for Lobectomy in Bronchiectasis** (movie in color) (abstract).—My purpose in showing this movie was not to demonstrate anything new or unusual, but merely to emphasize the fact that we, as general surgeons, have relegated the specialty of thoracic surgery to so-called specialists in this field, which was developed originally by general surgeons, because, after all, only the well-founded principles of general surgery are applicable, and I think we are grossly negligent not to emphasize and discuss thoracic problems more often than we do. I am presenting here the technique that I used in 8 cases with bronchiectasis which was limited to one lobe or more, 5 of which had bilateral lower lobe infection. In 2 patients the pathology was limited to the lower lobe (unilateral). One was a patient with all three lobes involved on the right.

I prefer the tourniquet method because: (1) it is simpler than the individual ligation of vessels and bronchus; (2) it is dangerous to attempt individual ligation in the presence of edematous inflammatory tissue; (3) it is not necessary to resect the involved lobe or flush with the hilum; (4) on account of the likelihood of a bronchial fistula developing, it is quite natural that a smaller bronchus would occlude much quicker than a larger and more rigid tube.

I might re-emphasize pertinent points of this technique. As you will note, the incision is a postlateral one, paralleling the seventh intercostal space and extending to the anterior axillary line. Segments of the seventh and eighth ribs are removed posteriorly, thus allowing the maximum spreading of the ribs. After the involved lobe is freed of its adherent attachments and the pulmonary ligament is severed, a tourniquet is applied to the hilum. A pleural cuff is developed and thence the lung is excised by gradually cutting in a circular manner within a few centimeters of the tourniquet. The stump is occluded with interrupted

chromic catgut, after which the raw surface of the stump is covered with the previously prepared pleural cuff. Two catheters are inserted inferior to the incision. The anterior one is used to withdraw the encased air and is removed in from eighteen to twenty-four hours. The posterior catheter remains in place indefinitely. Closure is carried out by reapproximating the ribs with interrupted black silk. The muscles are closed in layers with catgut and the skin with silk. It is also noted that these patients are all transfused during operation.

I would like to mention one other patient who had bronchiectasis associated with squamous carcinoma of the bronchus. In this case individual ligation technique was followed.

These patients range in age from 6 to 55 years. Five were males and 4 were females. The cause of pathology in 4 of these cases was due to aspiration of foreign bodies, 2 represented questionable congenital cystic diseases of the lung, 2 developed falling measles and whooping cough, and 1 was the malignancy which was mentioned above.

Of these patients there are 5 complete cures, but the other 4 had bilateral involvement prior to operation and are now being followed for the possibility of doing further surgery.

Discussion: **Michael DeBakey,** New Orleans, stated that he and his co-workers previously employed the technique of tourniquet ligation as described by the essayist, but more recently have used individual ligation of the hilar structures. It was found that the incidence of pleural infections was diminished and the postoperative stay in the hospital considerably decreased. **J. A. Kirtley, Jr.,** Nashville, asked Sanger if he left the tourniquet on. **I. A. Ferguson,** Atlanta, asked if Sanger ever crushes the phrenic nerve.

Sanger, in closing, stated that the point DeBakey made about hospitalization is well brought out. The last patient he had was discharged in three weeks. They have found that patients may leave the hospital unusually early. If they have inflammatory tissue, it is rather hazardous to try individual ligation. At the same time, he believed that, if bronchial infection is present, it should be done. He thought the other method is simpler. He never leaves the tourniquet on.

Michael DeBakey, New Orleans (Leader): **Round-Table Discussions on Suture Material and Wound Healing** (abstract): **DeBakey** prefaced the discussion by stating that the purpose of the round table was to present an opportunity for the members to discuss informally some surgical subject previously selected of current interest. Such a discussion would permit members of various sections to express their opinions and experiences and help crystallize a more rational comprehension and perhaps allow a better evaluation of the subject.

Because of the recent revival of interest in suture material, it was selected for this discussion. In the surgical service at Tulane University they had previously employed catgut and this was followed by the use of silk. On the basis of extensive experimental studies done in the Experimental Laboratory at Tulane by Alton Ochsner and Wm. Meade, it was found that cotton was the most desirable suture material. This was verified clinically and at present cotton is used exclusively. The advantages of cotton are that it produces minimal tissue irritation, is pliable and easily sterilized, is of sufficient strength in appropriate sizes, and is economical. Its tensile strength in tissue decreases considerably less than catgut, silk, or linen.

In clinical practice it should be realized that Halsted's rules regarding the use of silk must be strictly adhered to in the use of cotton. Ordinary spool cotton thread as bought in a notion store is employed. It is prepared by wrapping it on

rubber tubes and autoclaving it for fifteen minutes at 15-pound pressure or by boiling for twenty minutes. For ligation of small vessels in the subcutaneous tissue or other areas, No. 60 or 80 is used. For approximation of the peritoneum or fascia, "quilting cotton" is employed. A heavier material is rarely necessary, but occasionally No. 10 mercerized crochet cotton may be required. **Samuel McLanahan,** Baltimore, asked about cotton in the face of infection. **DeBakey** stated that on the basis of their experience one of the most important uses of nonabsorbable suture material is in contaminated wounds. Cases in which cotton was used in severely infected wounds have been observed to heal without sinus formation or the extrusion of the sutures. Apparently this complication is less likely to occur with cotton than with silk. Moreover, the use of a nonabsorbable suture material in the presence of infection is considered more desirable than the use of absorbable material because wound disruption is believed to be more likely with the latter for two reasons; first, the infection delays wound healing; and second, the liberated proteolytic ferments cause early digestion of the suture material. **John V. Goode,** Dallas, stated that he has used cotton ever since an article appeared in the *Journal of the American Medical Association,* in which a case was described of a colored woman who had the external carotid tied and no cotton came out in spite of wound infection. An important advantage is that it can be so easily sterilized. He stated that in a case in which the ovaries were removed the skin edges were closed with a subcuticular piece of cotton. It has now been six months and a little piece of cotton is still there and there has been no reaction. He has watched this with a great deal of interest. **Donald Donaldson,** Birmingham, Ala., asked if silk is used to close the peritoneum and if continuous sutures are ever used. **DeBakey** answered that cotton is used all the way through and that interrupted sutures are used exclusively. He emphasized the importance of cutting the suture down on the knot. To facilitate this a special suture scissors has been devised and was described in the J.A.M.A. **112**: 2410, 1939. **Richard T. Shackelford,** Baltimore, stated that one other suture material has been overlooked and that is alcohol-preserved fascia. Not many surgeons use it. Their experience has been that there is considerable accumulation of fluid interfering with the healing of the wound. Probably fascia is not used in the proper way. He and his associates have used it a great deal. This includes about 185 to 190 hernia patients. Experience has shown that, if the fascia is properly soaked before the time of operation, accumulation of secretion does not occur. If an operation is to be done at 9:00 A.M., the nurses place the alcohol-preserved fascia in a basin of salt solution as soon as they enter the operating room at 7:30, one and one-half hours before time to start the operation. Then it is changed to a fresh basin of solution and left there until 9:30 or 9:45. Frequently in large postoperative hernia one saves a great deal of time by not having to make a long incision in the thigh to obtain autofascia. There are many times when one cannot dissect a section of the rectus sheath. Alcohol-preserved fascia can solve a lot of these difficulties, and the secret of its proper use is the elimination of the chemical element. They have used it on animals and in human beings and have seen little, if any, difference in any way in the healing with alcohol-preserved fascia and autofascia.

Alfred Blalock, Nashville: **Activities of National Research Council in Preparedness** (abstract).—At the request of the Surgeon-General of the Army and Navy, the Division of Medical Sciences of the National Research Council has appointed certain committees which are acting in an advisory capacity. The talk consisted of a brief description of the activities of the Committees on Shock and on Surgery.

James R. Dawson, Jr., Nashville: **Some General Aspects of Antirabic Immunization of Dogs** (abstract).—Rabies in dogs can be controlled most satisfactorily by prophylactic immunization. Vaccines available at the present time are extremely variable in their effectiveness. The ideal vaccine, theoretically, would be one which would immunize as a result of a mild nonfatal attack of rabies. Experiments are reported in which rabies virus, propagated in the brains of chick embryos, was used to vaccinate rabbits successfully against large test doses of street and of fixed rabies virus.

Ann Minot and **Katharine Dodd**, Nashville: **Fluid Equilibrium** (abstract).—The blood volume may be seriously reduced (1) by excessive loss of fluid and (2) by an inability to attract and hold sufficient water in the blood stream because of a primary lack of plasma protein or because of a progressive loss of protein through injured capillaries. In simple dehydration fluid equilibrium can be restored by replacement of solutions of the appropriate electrolytes. When there is a deficiency of protein in the blood stream, protein as well as fluid must be restored before a normal distribution of body fluid can be maintained.

George S. Johnson, Nashville: **The Treatment of Carcinoma of the Jaw** (abstract).—A series of cases of carcinoma of the jaw were reported in which operation had been carried out. Approximately one-half of this series were alive and well between two and five years after operation.

Barney Brooks, Nashville: **Effects of Pressure and Temperature on Ischemic Necrosis** (abstract).—It is generally known that varying degrees of stress and strain exist in normal tissues and that unusual amounts of intermittent or constant pressure applied to tissues produce pathologic changes. The effects of different amounts of pressure applied for different lengths of time upon the various tissues of the living animal are not definitely known. The tail of the rat is particularly well adapted for the experimental study of this problem, because the animal may be easily restrained and the tail contains so large a number of different structures readily subjected to known pressures for measured lengths of time.

In a series of experiments it was found that the amount of pressure and the length of time necessary for producing massive necrosis were remarkably constant in healthy animals kept at ordinary room temperature.

The pathologic changes produced by amounts of pressure or periods of time short of that necessary for massive necrosis were also studied. Epithelial hyperplasia, fibrosing myositis, and nerve degeneration were observed.

Modification of the temperature of the tissues during periods subjected to pressure was found to be a powerful determinant of the length of time necessary for pressure to produce massive necrosis.